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VOLUME 31 NUMBER 3

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MARCH, 1934

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $8.00

Entered as Second-Class Matter, Jan. 7, 1919, at the Postoffice at Chicago, Illinois, Under the Act of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of Oct. 3, 1917, authorized Jan. 15, 1919.

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Archives of Neurology and Psychiatry

VOLUME 31 MARCH, 1934 NUMBER 3

LABYRINTH AND CORTEX

THE ELECTRENCEPHALOGRAM OF THE CORTEX IN STIMULATION OF THE LABYRINTH

E. A. SPIEGEL, M.D.

PHILADELPHIA

The labyrinth not only is a sense organ which regulates the equilibrium through many reflexes on striated muscles but is one of the most important receptors for the perception of position and movements. Even if optic impulses are shut out and disturbances of equilibrium are prevented by fixation of the head and of the body on the rotating chair, stimulation of the semicircular canals by rotation produces typical perceptions and delusions of movement and position (Fischer and Kornmüller [1]). Labyrinthine impulses are able even to alter sensations which take origin in other receptors, for instance, tactile sensations. A person sitting in a Bárány chair and touching the floor with the foot immediately after rotation believes that the foot moves on the ground (*Tastschwindel,* Purkinje [2]). This example shows that a cortical process such as the perception of a tactile sensation is modified by stimulation of the labyrinth. Furthermore, impulses from this organ can influence the structure of dreams (Eisinger and Schilder [3] and Hoff [4]) or of certain psychoses (Epstein [5]). Finally, vertigo similar to that produced by stimulation of the labyrinth can be observed in cerebral diseases, in the aura of epileptiform convulsions. All these facts make it probable that labyrinthine impulses can enter the cortex.

Vestibulocerebral pathways, however, could not be traced with certainty farther than the midbrain. I have studied, therefore, the conduc-

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Read by title at the Fifty-Ninth Annual Meeting of the American Neurological Association, Washington, D. C., May 9, 1933.

1. Fischer, M. H., and Kornmüller, A. E., in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie mit Berücksichtigung der experimentellen Pharmakologie, Berlin, Julius Springer, 1930, vol. 15, p. 442.

2. Purkinje, J. E.: Beyträge zur näheren Kenntnis des Schwindels aus autognostischen Daten, Med. Jahrb. d. k. k. österr. Staats **6**:79, 1820.

3. Eisinger, K., and Schilder, P.: Monatschr. f. Psychiat. u. Neurol. **73**:314, 1929.

4. Hoff, H.: Monatschr. f. Psychiat. u. Neurol. **71**:366, 1929.

5. Epstein, A. L.: Ztschr. f. d. ges. Neurol. u. Psychiat. **143**:759, 1933.

tion of labyrinthine impulses to the cortex by localized application of strychnine [6] on its different areas. This method increases the excitability of cortical sensory centers for the impulses entering from the respective sense organs (Baglioni and Magnini,[7] Dusser de Barenne [8] and Clementi [9]). I [6] found that stimulation of the labyrinth induced epileptiform convulsions in cats and dogs in which the posterior suprasylvian and ectosylvian gyri were strychninized, whereas after strychninization of the parietal or of the frontal lobe the stimulation of this sense organ had no such effect. It was concluded that the labyrinth is represented in the cortex and that its cortical localization is to be sought in parts of the temporal lobe. If this region is hyperexcitable, the labyrinthine impulses which enter here can radiate to contiguous motor centers and produce epileptiform convulsions. Aronson [10] confirmed these experiments and showed furthermore that impulses from each labyrinth can reach the opposite as well as the homolateral cortex. Extirpation of the cerebellum (Spiegel [6]) or severance of the posterior longitudinal fasciculus (Aronson [10]) did not prevent the epileptiform convulsions induced by stimulation of the labyrinth in the strychninized animals.

It seemed desirable to ascertain whether labyrinthine impulses enter the cortex, also if its excitability is not increased by strychninization. To answer this question the electrical disturbances called forth in the cortex by stimulation of the labyrinth were studied, as it is known, since the experiments of Caton,[11] that the electrical potentials of the cortex are changed by stimulation of sensory nerves or sense organs. Although there exists an extensive literature dealing with the effect of sensory impulses on the electrical potentials of the cortex,[12] so far as I know the electrencephalogram [13] in stimulation of the labyrinth has not been studied.

METHOD

The experiments were performed on forty-three cats and one Macacus rhesus. In the morning a cannula was inserted under ether anesthesia in the trachea and another in the external jugular vein; the temporal muscle was excised on one or both sides, and the skull was trephined above the areas to be studied. In some experiments, also, certain gyri were extirpated, as will be described later, or the bulla ossea of the middle ear was exposed and opened to prepare for subsequent

6. Spiegel, E. A.: Ztschr. f. d. ges. Neurol. u. Psychiat. **138**:178, 1932; J. Nerv. & Ment. Dis. **75**:504, 1932.

7. Baglioni, S., and Magnini, M.: Arch. di fisiol. **6**:240, 1909. Baglioni, S., and Amantea, G.: Arch. di farmacol. sper. **17**:302, 1914.

8. Dusser de Barenne, G. D.: Quart. J. Exper. Physiol. **9**:355, 1916.

9. Clementi, A.: Arch. di fisiol. **27**:356 and 388, 1929.

10. Aronson, L.: J. Nerv. & Ment. Dis. **78**:250 (Sept.) 1933.

11. Caton, R.: Brit. M. J. **2**:278, 1875.

12. See the historic review given by M. H. Fischer (Arch. f. d. ges. Physiol. **230**:161, 1932).

13. This term was first used by H. Berger (Arch. f. Psychiat. **87**:527, 1929) for the graphs of the cortical potentials.

destruction of the labyrinth. One small splint of bone, from 2 to 3 mm. in length and width, was carved out from the roof of the frontal sinus, and another from the bone above the area to be studied, which served later to fix the electrodes in position. Then the trephined bone was replaced or the gap of the cranium was closed by bone wax, the skin was sutured, and the animal was allowed to recover for several hours from the operation and the ether anesthesia. In the afternoon the labyrinth was stimulated, and the action currents were recorded during bulbocapnine catalepsy (usually from 0.05 to 0.1 Gm. of bulbocapnine hydrochloride by subcutaneous injection) or during curare paralysis (from 8 to 10 cc. of 1 per cent curare by intravenous injection). In some experiments it was necessary to inject a few cubic centimeters of curare a second time.

The labyrinth was stimulated by rotations (from ten to fifteen times), which seems the most physiologic method. An iron bar ending in a crank on one side and in a point on the other side was fixed on the animal board in its longitudinal axis. This bar, with the animal board, could be set in a framework in such a way that the animal and the board, which were held in vertical position with the head upward, could be easily rotated around the longitudinal axis. Special care was taken to fix the head rigidly and to fasten the trunk by a bandage on the board to avoid any movement of the head and of the whole animal other than the rotation around the longitudinal axis.

The recording electrodes were silver wires, insulated with paraffin or de Khotinsky cement, with the exception of the tip, and coated with silver chloride. They were fastened on the inside of the splints, which were prepared in the morning above the areas to be studied. The dura was opened in some experiments; in others it remained closed, as the action currents could be led off through the dura and the brain was better protected. After fixing the electrodes in place, the gap in the bone was closed again, by setting in the trephined bone and by bone wax, as much as was possible without interfering with the electrodes. The diffuse electrode was fastened on the splint already mentioned in the roof of the sinus frontalis. It was a silver wire ending in a small silver plate and was also insulated with the exception of the part touching the bone splint. It is of special importance in such experiments that movements not only of the head in relation to the animal board but also of the electrodes are absolutely avoided. A framework was therefore fixed on the animal board to fasten the electrodes and the insulated copper wires which were soldered on them. These wires led to a connecting plug fixed on a post of the animal board. The animal had to be disconnected from the galvanometer during rotation and as quickly as possible connected with it again at the end of rotation. This was easily accomplished by the use of another connecting plug, which fitted into the sockets of the first and the wires of which led to the string galvanometer. Also the artificial respiration which was necessary in the curarized animals had to be interrupted during rotation by disconnecting the supplying hose from the tracheal cannula. It could easily be replaced immediately after rotation.

As the recording instrument, a string galvanometer with amplifier constructed by the Sanborn Company was used. This apparatus has, according to the description given by the company, a specially designed magnet gap for accommodating various lengths of galvanometer strings. The field is energized by a high capacity storage battery with a potential of 6 volts at about 2.5 amperes, a total energy consuming about 15 watts. The galvanometer strings are of two lengths, 7 cm. for comparatively low speed recording and 3 cm. for rapid speed response. The fibers are gold-plated quartz of from 2,000 to 5,000 ohms with a diameter of from 2 to 4 microns.

The instrument may be used and standardized either with or without an amplifier. It is built for from three to five tubes; usually, however, only three tubes were used as the amplification was sufficient. The tubes are connected by resistance coupling; the output of the amplifier is fed through a high capacity condensor, thus protecting the string circuit and keeping plate potential off the string.

Special nonmicrophonic tubes are used (listed as RCA Radiotron 864). They have an amplification factor of about 6 per tube so that three tubes in cascade have an amplification up to about 200, carying with the resistance of the string. In the present investigation amplification up to about 50 was used. High intertube capacities permit the amplification of very low frequencies. The amplifier is practically uniform throughout a range of from 30 to 7,000 cycles per second. It is supported by a spring suspension and is electrically shielded by a double thickness of metal and acoustically shielded by felt. It can be connected either with the string galvanometer or with a phone or a loud speaker. The camera is mounted on a second cabinet, separated 2 inches (5 cm.) from the galvanometer unit; it operates at various speeds from 2.5 mm. per second to 500 mm. per second. It is belt-driven by carefully filtered direct current motor operating on 110 volts, direct current. Provision is made for using 6 cm. perforated bromide paper or film and also 35 mm. bromide paper or film. The magazine container is sufficient for 200 feet of paper; the removable record box will contain the entire magazine if required. In order to prevent electrical interference the timer is operated from compressed air. Various speeds of timing are possible up to hundredths of a second.

The whole galvanometer with the rotating apparatus and the operator with his assistant were surrounded by a Faraday cage, which was grounded and prevented the interference of extraneous currents.

RESULTS AND COMMENT

The electrencephalogram of the resting brain, i. e., in an animal without application of artificial stimuli, shows oscillations of smaller and larger amplitude, as recorded by Práwdicz-Neminski,[14] Berger,[15] Bartley and Newman,[16] Travis and Dorsey[17] and others. Such smaller and larger oscillations were found in the present investigation in the curarized animals as well as during bulbocapnine catalepsy. Berger[15] called the larger waves α and the small one β waves. According to him, the α waves show a periodicity similar to Wundt's apperception waves, and their amplitude is lowered in sleep. He observed only the β waves when the cortical area from which the electrodes led off was disconnected from other parts of the brain, e. g., by an underlying tumor. This is in agreement with some records made in the present experiments, as the larger waves were missed in deep narcosis (fig. 1 *A* and *B*) and more or less

14. Práwdicz-Neminski, W. W.: Arch. f. d. ges. Physiol. **209**:362, 1925.

15. Berger, H.: Arch. f. Psychiat. **87**:527, 1929; **94**:16, 1931; J. f. Psychol. u. Neurol. **40**:160, 1930.

16. Bartley, S. H., and Newman, E. B.: Am. J. Physiol. **99**:1, 1931.

17. Travis, L. E., and Dorsey, J. M.: Action Current Studies of Simultaneously Active Disparate Fields of the Central Nervous System of the Rat, Arch. Neurol. & Psychiat. **28**:331 (Aug.) 1932.

diminished after incision into the white matter below the area in which the currents were recorded (fig. 3 *C*). Berger drew the inference that α waves accompany such processes in the cortex as are called psychophysical and as may be eventually associated with phenomena of consciousness; he thought that the β waves are merely an expression of vital processes in the brain tissue. This interpretation is mentioned here because the α waves as well as the β waves are found on the electrencephalogram of cats in bulbocapnine catalepsy. If Berger's interpretation is correct and applicable to the cat's brain, this finding means that such cortical processes as are called psychophysical are still present in this special form of experimental catalepsy.[18]

The chief question to be answered was whether the electrencephalogram of the resting brain is changed if the labyrinth is stimulated by

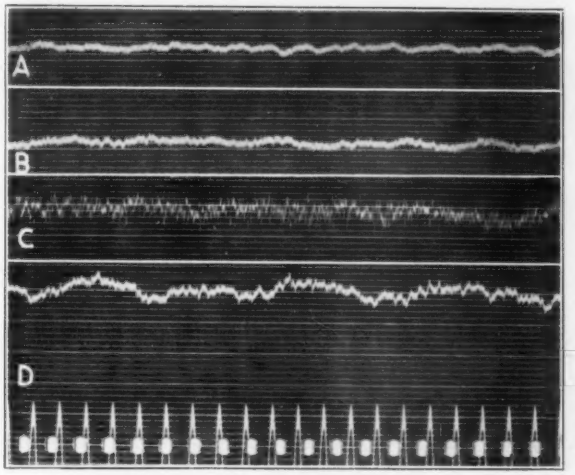

Fig. 1 (cat 6).—Electrencephalogram from the left posterior ectosylvian gyrus. *A* was taken after fifteen rotations to the right (in the dark), during ether narcosis; *B*, with the animal resting. *C* was taken after fifteen rotations to the right (in the dark), during bulbocapnine catalepsy (0.05 Gm. of bulbocapnine hydrochloride); *D*, with the animal resting. The eyes were open; the dura was not opened; 0.1 mv. = 3 mm. The time marker indicates one-tenth second intervals.

rotation. Figure 1 shows such an experiment on a cat in bulbocapnine catalepsy. The animal is still under ether anesthesia, and there is no difference between the graphs taken from the left posterior ectosylvian gyrus before and after the rotation (fig. 1 *A* and *B*). This is in agreement with the experience of Fleischl [19] and Beck [20] on the cortex and

18. A more detailed study of the electrencephalogram in bulbocapnine catelepsy will be given elsewhere.

19. Fleischl, E.: Zentralbl. f. Physiol. **4**:537, 1890.

20. Beck, A.: Zentralbl. f. Physiol. **4**:473, 1890; Arch. f. d. ges. Physiol. **155**: 461, 1914.

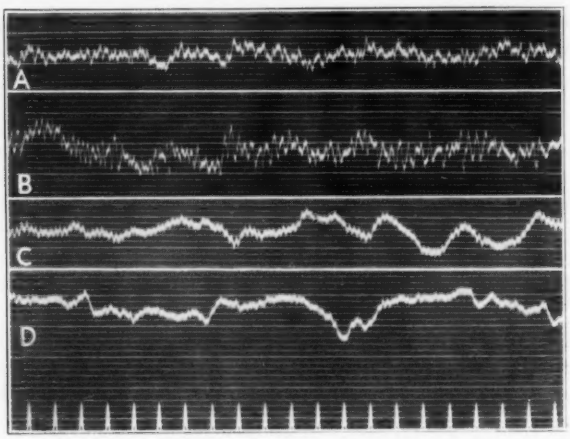

Fig. 2 (cat 7).—Electrencephalogram made during bulbocapnine catalepsy (0.05 Gm. of bulbocapnine hydrochloride). The testing electrode was on the posterior suprasylvian sulcus. The dura was not opened. *A* was taken with the animal resting, before labyrinthectomy; *B*, after fifteen rotations. *C* was taken with the animal at rest, after bilateral labyrinthectomy; *D*, after twenty rotations. The eyes were open; rotation was done in the dark; 0.1 mv. = 3 mm. The time marker indicates tenth second intervals.

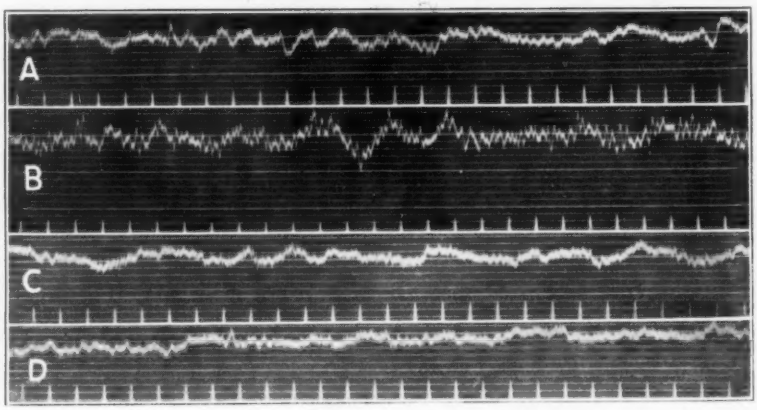

Fig. 3 (cat 25).—Transverse section of the spinal cord at the second cervical segment was performed. The testing electrode was at the posterior suprasylvian gyrus. Curare paralysis was produced. *A* was taken with the animal resting; *B*, after fifteen rotations to the right. *C* was taken with the animal resting, after incision below the posterior suprasylvian gyrus; *D*, after fifteen rotations to the right. The dura was closed when *A* and *B* were taken and open when *C* and *D* were taken; 0.1 mv. = 4 mm. The time marker indicates one-tenth second intervals.

of Forbes and Miller,[21] and Saul and Davis [22] on the brain stem that stimulation of sensory nerves produces very weak, if any, electrical disturbances in the central nervous system if the animal is in narcosis. After recovery of the animal from the ether (fig. 1 *C* and *D*) the amplitude of the oscillations is distinctly increased after rotation (3 — 6 mm. = 0.1 — 0.2 mv.) in comparison with the finding in the resting animal (from 1 to 2 mm.).

With regard to the latent period between the end of the rotation and the beginning of the change of the electrencephalogram, it cannot be said what happens in the first second after the rotation, as it took about one second to connect the animal with the string. In some animals the graphs showed the increase of the oscillations as soon as the record started; in others several (from three to four) seconds elapsed before such a change was noticed. Also the duration of this increase varied from two to fourteen seconds. A continuous increase of the amplitude is rarely observed; usually larger waves appear in groups which are separated by periods of from two-tenths to nine-tenths of a second, in which only small waves are recorded.

The question arose whether these changes of the electrencephalogram are due to impulses which originate in the labyrinth. Hence, in some experiments the bulla ossea of the middle ear was exposed from the neck; the middle ear was opened so that a good view of the promontorium resulted. Figure 2 shows the effect of the rotation on the electrencephalogram of such a cat. The animal is again in bulbocapnine catalepsy; one electrode is fixed to the frontal bone, the other above the dorsal part of the posterior suprasylvian sulcus, between the posterior ectosylvian and suprasylvian gyri. The increase of the amplitude of the oscillations, which shows here a grouping of the impulses as already described, is marked (maximum deflection before rotation 4 mm., after rotation, 7 mm.). After this graph was recorded the promontorium was opened and the labyrinth destroyed; the remaining nerves were killed by small cotton sponges soaked with 40 per cent formaldehyde. After this bilateral labyrinthectomy, rotation of the animal (even twenty times) produced no more change in the recorded currents.

The next problem was to analyze whether the electrical disturbances led off after rotation were really due to an excitation of the cortex. The experience that narcosis suppresses them was in favor of such an interpretation. It was possible, however, that the observed changes of the graphs were due to a spread from muscular action currents, from subcortical regions of the central nervous system or from the labyrinth. Although bulbocapnine suppresses voluntary movements to a large

21. Forbes, A., and Miller, R. H.: Am. J. Physiol. **62**:113, 1922.

22. Saul, L. J., and Davis, H.: Action Currents in the Central Nervous System, Arch. Neurol. & Psychiat. **28**:1104 (Nov.) 1932.

extent, it does not abolish labyrinth reflexes on the ocular or skeletal muscles; stronger excitation of the animal may even result in movements. Hence, it was necessary to continue the experiments after paralyzing the motor endings with curare. Figures 3, 4 and 6 show that even in such a paralysis a distinct increase of the amplitude of the deflections can be noticed after rotation. In experiment 25 (fig. 3), for instance, a measurement of the deflections shows in the resting animal within one second only one oscillation, of 3 mm. amplitude; all other oscillations were between 1 and 2 mm.; after rotation, within one second eight deflections of 3 mm. and three deflections of 4 mm. were observed (4 mm. = 0.1 mv.). Intermittent patterns again prevailed, the larger oscillations appearing in groups which were separated by shorter or longer intervals of smaller fluctuations. It is interesting in this con-

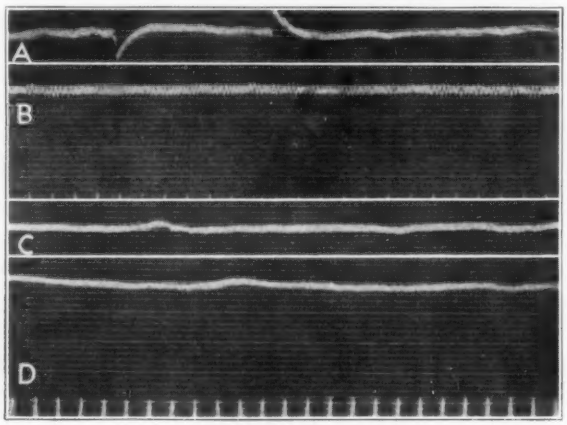

Fig. 4 (cat 27).—Paralysis was caused with curare; a lesion of the parietal lobe was produced (see fig. 5). The testing electrode was on the posterior ectosylvian gyrus. The dura was opened. The eyes were closed. *A* was taken with the animal resting; standardization with 0.1 mv.; *B*, after fifteen rotations to the right. *C* was taken with the animal resting, after incision into the posterior ectosylvian gyrus below the electrode (see fig. 5); *D*, after fifteen rotations to the left. In this experiment 0.1 mv. = 3.5 mm. The time marker indicates one-tenth second intervals.

nection that even single stimuli to a sensory nerve may elicit a cortical response the amplitude of which rises and falls with a slow rhythm, as was shown by Bartley and Bishop [23] in stimulation of the optic nerve. The objection that the currents recorded after rotation may be due to a spread from the labyrinth or from subcortical ganglia can also be invalidated. After incision into the white matter below and parallel to the cortical area from which the currents were led off, the rotation failed

23. Bartley, S. H., and Bishop, G. H.: Proc. Soc. Exper. Biol. & Med. **29:** 775, 1932.

to increase the currents in curarized animals, though it had such an effect before the incision (figs. 3 and 4). If the currents were due merely to a spread from the subcortex or from the labyrinth, such spreading currents should be observed also after the severance of the corticopetal fibers.

It has already been mentioned that the postrotatory increase of the cortical currents was not observed after bilateral labyrinthectomy. In agreement with this it was found that the rotation produced the aforementioned changes of the electrencephalogram in animals with a normal labyrinth also if the eyelids were closed. To avoid errors due to retinal impulses, the eyelids were held shut by adhesive tape in the majority of the experiments. Another group of accessory stimuli, however, also had to be considered. As the labyrinth acts not only on striated muscles but also on vegetative organs, it seemed possible that impulses from

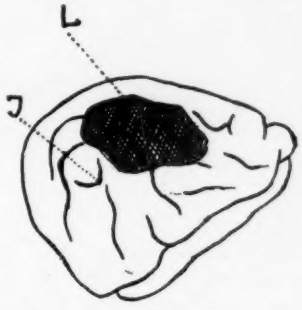

Fig. 5 (cat 27).—*L* indicates the lesion of the right middle ectosylvian and suprasylvian gyri and partly of the lateral gyrus. *J* indicates the incision below the electrode.

internal organs which are excited from the labyrinth may play a rôle in the postrotatory changes of the electrencephalogram. Control experiments showed that bilateral vagotomy or a high transverse section of the spinal cord does not prevent the increase of the cortical currents in the posterior suprasylvian and ectosylvian gyri following stimulation of the labyrinth (fig. 3). Consequently these changes of the electrencephalogram are not due to centripetal impulses from the viscera, which may reach the brain with the vagi or with afferent fibers of the splanchnic and ascending tracts of the cord. A high transverse section of the cord also prevents vestibulovascular reflexes, as shown by Spiegel and Démétriades;[24] thus it can be excluded that a fall of blood pressure and consequent anemia of the brain are the causes of the observed increase of the cortical currents. As already mentioned, the artificial respiration

24. Spiegel, E. A., and Démétriades, T.: Arch. f. d. ges. Physiol. **196**:185, 1922.

which was applied in the experiments with curare had to be stopped during the rotation, i. e., for from ten to twelve seconds. Control experiments showed that interruption of the artificial respiration for the same interval practically did not change the electrencephalogram of a resting animal.

These experiments seem to justify the conclusion that labyrinthine impulses can enter the cortex and produce a change of its activity even if its cells are not in a state of hyperexcitability as in the aforementioned experiments with strychnine. The further question arose whether the study of the electrical potentials may be used to determine the areas where the labyrinthine impulses enter the cerebral cortex. Three regions have been considered as the possible destinations of vestibulocerebral pathways: the frontal lobe, the parietal lobe and the temporal lobe. My aforementioned experiments with strychnine made it probable that a cortical center of the labyrinth is to be sought in the posterior suprasylvian and ectosylvian gyri, i. e., in parts of the temporal lobe. If one studies this question by records of the postrotatory cortical action currents one meets the following difficulty. During rotation the labyrinth is stimulated, and impulses from this organ not only can reach the cortex, but also can radiate here from the place of entrance into different areas, before the rotation is stopped. If one wants to ascertain where the labyrinthine impulses enter the cortex by records of the action currents after rotation it is, therefore, necessary to combine such experiments with extirpation of the various areas to be studied.

To begin with the parietal lobe, the changes of potential led off from here after rotation were in some experiments no longer noticed if the posterior ectosylvian and suprasylvian gyri were extirpated or an incision was made between the middle and posterior part of the ectosylvian and suprasylvian gyri. In other cases these operations were not sufficient, and rotation still increased the currents in the parietal lobe. After combined extirpation of the posterior ectosylvian and suprasylvian gyri and of the frontal lobe with the sigmoid gyri and the anterior part of the coronal gyrus, however, the rotation had no effect on the action currents of the parietal lobe. Consequently the postrotatory changes in the electrencephalogram of this lobe ought to be considered as due to currents or impulses which originate partly in the posterior suprasylvian and ectosylvian gyri and partly in the frontal lobe. The parietal lobe can be dispensed with in order to record postrotatory action currents in the posterior suprasylvian and ectosylvian gyri. Figures 4 and 5 show such an experiment; the potentials led off from the posterior ectosylvian gyrus are increased after rotation, although the middle suprasylvian and ectosylvian gyri and an adjacent strip of the lateral gyrus are extirpated. The weakness of the reaction is apparently due to the

fact that the large contiguous cerebral lesion impaired the blood supply and thus the function of the area under study.

Analysis of the currents picked up from the frontal lobe served first to ascertain whether the postrotatory increase is due merely to an irradiation of the impulses from the posterior parts of the cortex. The experiments with strychnine had shown that such an irradiation from the posterior suprasylvian and ectosylvian gyri to the motor centers of the cortex is possible, and that epileptiform convulsions may result after stimulation of the labyrinth if the posterior suprasylvian and ectosylvian gyri are hyperexcitable.

Experiments were therefore performed in which the effect of rotation on the action currents of the frontal lobe was studied after bilateral

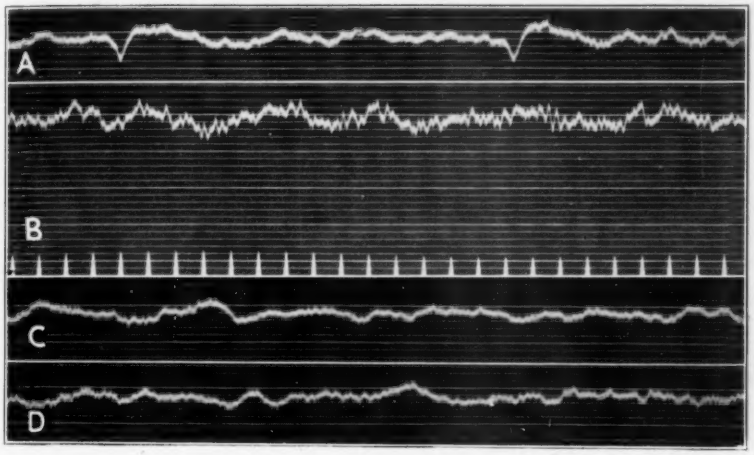

Fig. 6 (cat 32).—Curare paralysis was produced; a lesion of the frontal lobe and motor area was carried out (see fig. 7). The testing electrode was on the posterior suprasylvian gyrus. The dura was opened. The eyes were closed. *A* was taken with the animal resting (the two large oscillations are due to respiratory movements of the brain); *B*, after fifteen rotations to the right. *C* was taken with the animal resting, after incision into the posterior suprasylvian gyrus below the electrode (see fig. 7); *D*, after fifteen rotations to the left. In this experiment, 0.1 mv.= 4 mm. The time marker indicates one-tenth second intervals.

extirpation of the posterior suprasylvian and ectosylvian gyri. This operation did not prevent the postrotatory increase of potentials in the frontal lobe. It had therefore to be considered that besides the radiation from the posterior suprasylvian and ectosylvian gyri to the frontal lobe, impulses entering from lower levels of the brain could take part in the genesis of the electrical disturbance observed in the frontal lobe after rotation. These can be impulses from the labyrinthine nuclei, from

the spinal cord or from both sources. Dusser de Barenne [25] has shown by local strychninization that the sensory zone of the cerebral cortex includes also the so-called motor area. If impulses from the spinal cord enter the sigmoid gyri, the possibility must be considered that impulses from the spinal cord which reach these gyri can radiate into the premotor zone or that the electrical disturbances induced by such impulses from the cord in the sigmoid gyri spread into the frontal pole and are picked up by the electrodes. Therefore, the bilateral extirpation of the posterior suprasylvian and ectosylvian gyri was combined with a high transverse section of the cord; thus, a radiation of impulses from the posterior part of the cortex to the frontal lobe as well as the entrance of afferent impulses from the spinal cord into the sigmoid gyri or into the whole frontal lobe was prevented. After such combined operations rotation produced only very slight changes of the currents which were led off from the frontal cortex; these changes were within the variation

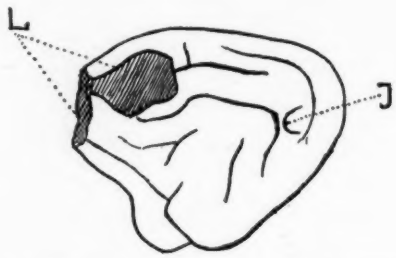

Fig. 7 (cat 32).—*L* indicates the lesion of the left frontal lobe and motor area; *J*, the incision below the electrode.

observed in the electrencephalogram of the resting brain. But it seems necessary to be careful if one draws conclusions from these experiments. Such combined lesions could lower the excitability of the remaining part of the central nervous system, and thus postrotatory changes of the electrical currents could be missed in the frontal lobe after these operations even though normally labyrinthine impulses could reach the frontal lobe. Still another point has to be considered. Magnus [26] and Rademaker [27] found that the nucleus ruber is the center of some labyrinth reflexes (the righting reflexes); my own experiments in cooperation with Nishio,[28] as well as the study of the fiber degeneration in dogs the

25. Dusser de Barenne, J. G.: Proc. Roy. Soc., London, s. B **96**:272, 1924; footnote 8.

26. Magnus, R.: Körperstellung, Berlin, Julius Springer, 1924.

27. Rademaker, G. G.: Die Bedeutung der roten Kerne und des übrigen Mittelhirns für Muskeltonus, Körperstellung und Labyrinthreflexe, Berlin, Julius Springer, 1926.

28. Nishio, S.: Arb. a. d. Neurol. Inst. a. d. Wien. Univ. **29**:60, 1927.

vestibular nuclei of which I had injured (Alexander and Whitaker [29]), showed that labyrinthine impulses, using the posterior longitudinal fasciculus, can reach the nucleus ruber. The connections of this nucleus with the cerebral cortex were studied by von Monakow,[30] who found that this nucleus sends impulses to the optic thalamus and further to the frontal lobe. These cortical connections of the nucleus ruber, however, are scanty in carnivores; they are more developed in monkeys and in man. The difficulty of proving functional connections of the labyrinth with the frontal lobe by a study of the electrical potentials in the cat might be due partly to the underdevelopment of the vestibulofrontal pathways in these animals.[31] It is possible that in animals with a better developed frontal lobe, in monkeys and particularly in man, the electrical changes in the frontal lobe following stimulations of the labyrinth will

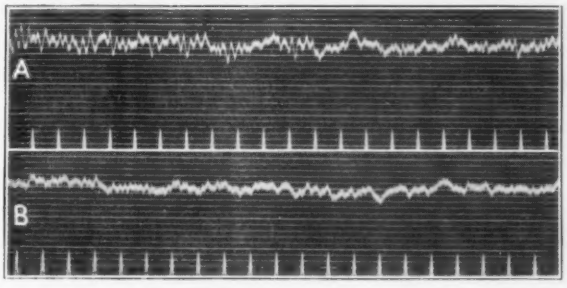

Fig. 8 (Macacus rhesus).—This animal was given 0.08 Gm. of bulbocapnine hydrochloride. The eyes were open. The dura was not opened. The testing electrode was between the caudal part of the sylvian fissure and the external parieto-occipital fissure. *A* was taken after fifteen rotations to the right; *B*, with the animal at rest. In this experiment 0.1 mv. = 3 mm. The time marker indicates one-tenth second intervals.

be more easily demonstrable. I hope that I shall soon be able to report such additional experiments on monkeys.

With regard to the temporal lobe, it has been mentioned that the postrotatory action currents led off from the posterior suprasylvian and ectosylvian gyri could be noticed even after closing the eyelids and after vagotomy, high transverse section of the cord or extirpation of the

29. Alexander, L., and Whitaker, J. G.: J. f. Psychol. u. Neurol. **44**:253, 1932.

30. von Monakow, C.: Arb. a. d. hirnanat. Inst. Univ. Zürich, 1910, nos. 3 and 4, p. 196.

31. Recently P. Bard and O. Orias (Am. J. Physiol. **105**:2 [July] 1933) studied the labyrinthine placing reaction of the forelegs which occurs when cats are lowered, head down, after enucleation of the eyes. This reaction depends on the intactness of the frontal and sigmoid gyri. This seems to indicate that at least some labyrinthine impulses reach the rostral poles of the brain.

parietal lobe. Further experiments showed that also the frontal lobe with the gyri sigmoidei and the anterior part of the coronal gyrus can be removed without preventing the appearance of postrotatory action currents in the dorsal part of the posterior suprasylvian and ectosylvian gyri (figs. 6 and 7). Control experiments (fig. 6 *C* and *D*) showed that such action currents no longer appeared if an incision was made into the white matter below and parallel to the last-mentioned gyri, so that they received no impulse from the subcortex. In seems, therefore, justifiable to assume that labyrinthine impulses can enter the dorsal part of the posterior suprasylvian and ectosylvian gyri, i. e., parts of the temporal lobe adjacent to the parietal lobe. Figure 8 shows that a postrotatory increase of the electrical potentials was also recorded from the dorsocaudal part of the temporal lobe, between the caudal part of the sylvian fissure and the external parieto-occipital fissure in a Macacus rhesus in bulbocapnine catalepsy. Definite conclusions for the brain of the monkey, however, must be postponed until experiments on such animals are possible on a larger scale.

SUMMARY

The changes of electrical potentials induced in the cortex by stimulation of the labyrinth were studied. Rotation increased the currents, which were led off from the dorsal part of the posterior suprasylvian and ectosylvian gyri in cats under curare paralysis or bulbocapnine catalepsy. Such an effect was not prevented if the eyes were closed, the vagi or the uppermost segments of the spinal cord were severed, or the frontal lobe with the motor zone or the parietal lobe was extirpated. In deep ether anesthesia, after bilateral labyrinthectomy or after an incision into the white matter severing the connection of the posterior suprasylvian and ectosylvian gyri with the subcortex, the electrogram of these gyri was not changed by rotation. A postrotatory increase of the potentials in the parietal lobe depends on the intactness of the posterior suprasylvian and ectosylvian gyri and of the frontal lobe; after combined extirpation of the frontal and the temporal lobe, rotation could no longer increase the currents led off from the parietal lobe. Postrotatory electrical disturbances were noticed in the frontal lobe even after extirpation of the temporal lobes, but a definite effect of the rotation was no longer observed if this extirpation was combined with high transverse section of the spinal cord. The experiments seem to indicate that labyrinthine impulses can enter the cortex, particularly parts of the temporal lobe near the parietal lobe. It is also possible that rubrothalamofrontal tracts are used as a common path by the labyrinthine as well as by other impulses. Further experiments on monkeys are planned to elucidate this point.

USE OF IODIZED POPPY SEED OIL IN DIFFERENTIAL DIAGNOSIS BETWEEN TUMORS OF CONUS MEDULLARIS AND OF CAUDA EQUINA

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It has been the experience of many observers that in cases of intraspinal tumor the information given by injection of iodized poppy seed oil 40 per cent may be misleading and deceptive. This observation, coupled with recent reports of toxic effects following iodolography, has led to a wave of condemnation of the use of iodized oils in the subarachnoid space. In this paper I present 4 cases of tumor of the conus medullaris or cauda equina as illustrations of the belief that in the diagnosis of tumors of this region the advantages of the use of iodized poppy seed oil outweigh objections to it.

DIFFERENTIAL DIAGNOSIS BETWEEN TUMORS OF THE CONUS MEDULLARIS AND CAUDA EQUINA

While clinical methods for the differentiation of lesions of the conus from those of the cauda are frequently given, actual experience will soon demonstrate their uncertainty. Cushing and Ayer [1] pointed out that the diagnosis of caudal tumors on the basis of their neurologic symptoms alone is not always easy. These authors have also shown that xanthochromic fluid may exist above as well as below a caudal tumor. They described a method of diagnosing subarachnoid block below a lumbar puncture by noticing incomplete pressure changes produced when saline solution is injected into the sacral hiatus. The use of multiple punctures to diagnose mechanically the exact site of a lumbosacral lesion of the cord has been advanced by Stookey and Klenke.[2] In certain vascular tumors such a procedure might be dangerous. Viets [3] has suggested that the presence of root pain on jugular compression might

From the Division of Neurology and Neurosurgery, University of Chicago.
Read at a Meeting of the Chicago Neurological Society, May 18, 1933.

1. Cushing, Harvey, and Ayer, J. B.: Xanthochromia and Increased Protein in the Spinal Fluid Above Tumors of the Cauda Equina, Arch. Neurol. & Psychiat. **10**:167 (Aug.) 1923.

2. Stookey, Byron, and Klenke, Dorothy: A Study of the Spinal Fluid Pressure in the Differential Diagnosis of Diseases of the Spinal Cord, Arch. Neurol & Psychiat. **20**:84 (July) 1928.

3. Viets, H. R.: Two New Signs Suggestive of Cauda Equina Tumors: Root Pain on Jugular Compression and Shifting of the Lipiodol Shadow on Change of Posture, New England J. Med. **198**:671 (May 17) 1928.

be used in the diagnosis of caudal tumors. In his patient the pain occurred only after the removal of fluid from below the tumor. However, root pain is not always an accurate indicator of the site of compresssion.

The usual description in textbooks [4] of the differential diagnosis between tumors of the conus and cauda illustrates the uncertain basis for such a clinical differentiation. In lesions of the conus, disturbances in the bladder and rectum are said to occur early and to be severe. Saddle anesthesia is characteristic, and a dissociation of sensation may be present. Only the ankle jerk is apt to be lost. Erection and ejaculation may be either lost or impaired. As the lesion is within the cord, fibrillations may be present. Pain is usually not severe and is limited to the perineum, bladder, rectum and upper portion of the thighs. The lesion is usually bilateral, and trophic changes may occur.

On the other hand, in lesions of the cauda, pain is the most prominent symptom. The pain may follow the nerve roots down the legs or perineum, or it may be limited to the small of the back. Saddle anesthesia may be present, and there is no dissociation of sensation. The paralysis is flaccid and may be associated with atrophy. If the lesion is low and bilateral it may affect the bladder and rectum, causing incontinence, but symptoms in the bladder are frequently absent, especially in higher lesions of the cauda. Both the patellar tendon and the achilles tendon reflexes are usually absent. The involvement is frequently asymmetrical, or it may remain unilateral for a long time. Recovery is more apt to occur than in lesions of the conus.

Oppenheim [5] gave several points of differentiation. He stated that pain and tenderness over the lower lumbar vertebrae are indicative of caudal lesions, but he mentioned many exceptions to this rule. Dissociation of sensation may mean a conus lesion, but its absence does not always mean a caudal lesion. The most important differential point is the intense pain of caudal lesions, which is usually but not always absent in conus lesions. A sudden onset is apt to indicate a conus lesion. In this regard it may be mentioned that Elsberg and Constable[6] differentiated between various lesions of the cauda alone by the rapidity or slowness of the onset. Oppenheim also stated that a marked asymmetry of the paralytic symptoms hardly ever occurs except in diseases of the cauda equina. Changes in the tendon reflexes are not an absolute sign. Absence of the achilles tendon reflex is the rule in diseases of

4. Wechsler, Israel S.: A Text-Book of Clinical Neurology, ed. 2, Philadelphia, W. B. Saunders Company, 1931, p. 173.

5. Oppenheim, H.: Lehrbuch der Nervenkrankheiten für Aerzte und Studierende, ed. 5, Berlin, S. Karger, 1908, vol. 1, p. 450.

6. Elsberg, C. A., and Constable, Kate: Tumors of the Cauda Equina: The Differential Diagnosis Between New Growth and Inflammatory Lesions of the Caudal Roots, Arch. Neurol. & Psychiat. **23**:79 (Jan.) 1930.

both the conus and the cauda, but the knee jerk is present and often exaggerated in the former, while it may be absent in a lesion of the higher part of the cauda.

Allen [7] discussed extensively the clinical features of tumors of the cauda equina. He stated that variations in sensation in the saddle area, even when they appear after sensory changes elsewhere, are found in less than one third of the cases of caudal tumor. Asymmetrical changes in sensation are found in 60 per cent of the cases. In caudal tumors the upper sensory level indicates the upper level of the tumor in only one half of the cases; in the other half the lesion is at a higher level. Whereas an absence of symmetrical involvement is generally considered to denote the presence of a caudal rather than a conus lesion, Allen pointed out that bilateral signs are more indicative of a caudal lesion than a true sciatica. He also stated that pain in the back is more significant of caudal tumors than is pain in a lower extremity.

Parker [8] stated that tumors in the lumbosacral canal present a completely different picture from that shown by tumors in the cervical and thoracic regions. Tumors at widely separated levels of the lumbosacral canal may give almost identical signs and symptoms. A tumor in the lumbosacral canal, where the first sacral root is as long as 14 cm., does not announce its position with exactitude. Parker presented 8 cases of tumor in this region in which it was difficult to make a differential diagnosis between tumors of the conus and of the cauda. He laid great stress on the relief of pain by activity. Five of the 8 patients had slept sitting in a chair for months, and when they were no longer able to walk remained day and night in the chair in which they were wheeled about. One patient had a permanent contracture of the hamstrings from such a position. Another patient spent nights kneeling on a chair and lying face downward across the table. In the early stages the patients soon discovered that movement relieved them, and while jarring and sudden movements increased the pain, on the whole they were more comfortable while walking.

Elsberg [9] pointed out that in tumors between the roots of the cauda equina it is often difficult, in spite of the use of clinical and manometric studies, to decide whether the growth lies near the origin from the cord of the affected spinal roots or farther caudad. He also stated that in these patients the exact vertebral level of the tumor can be determined

7. Allen, I. M.: Tumors Involving the Cauda Equina: A Review of Their Clinical Features and Differential Diagnosis, J. Neurol & Psychopath. **11**:111 (Oct.) 1930.

8. Parker, H. L.: The Diagnosis of Tumors of the Cauda Equina, Conus and Epiconus Medullaris. A Report of Nine Cases, Am. J. M. Sc. **63**:342, 1933.

9. Elsberg, C. A.: Tumors of the Spinal Cord: Problems in Their Diagnosis and Localization; Procedures for Their Exposure and Removal, Arch. Neurol. & Psychiat. **22**:949 (Nov.) 1929.

by a lumbar injection of iodized oil. Elsberg and Constable [6] discussed the differentiation between new growths and inflammatory lesions of the caudal roots. Many of the points of differentiation between these two types of caudal lesion are the same as are commonly used to discriminate between tumors of the conus and of the cauda. Farley [10] pointed out that not only is the differentiation between various levels difficult, but in many cases it is almost impossible even to diagnose the presence of a tumor in the lower spinal canal. He reported the case of a patient seen by 13 physicians and treated by spinal fusion before a diagnosis of caudal tumor was finally made.

Riser, Bezy and Boularan [11] reported the case of a woman, aged 62, with violent pain and abolition of tendon reflexes but without any sensory changes, in which iodized poppy seed oil correctly localized a tumor of the cauda equina. On the other hand, Hanse [12] reported an instance in which iodized poppy seed oil localized the level of a caudal tumor several segments too high. In the discussion of a paper by Globus and Strauss,[13] Stookey stated that the use of iodized oil is particularly indicated in tumors of the cauda equina because the neurologic signs are identical for a number of levels. Ayer stated in the same discussion that in tumors of the caudal region iodized oil will have an increasing usefulness, since the clinical study of these tumors is far from satisfactory.

USE OF IODIZED POPPY SEED OIL

The following histories are given as examples of this phase of the subject:

CASE 1.—*Pain in the lumbar region radiating down both legs. Xanthochromia above the tumor. Two unsuccessful laminectomies. Localization with iodized poppy seed oil. Third laminectomy. Biopsy and roentgen treatment of capillary hemangioma of the cauda equina. Slight improvement.*[14]

History.—L. S., a white man, aged 48, who was referred to the University of Chicago Clinics by Dr. Peter Bassoe of Chicago on Feb. 1, 1929, had first noted

10. Farley, O. L.: Two Cases Illustrating the Difficulties in the Diagnosis of Spinal Cord Tumors with Sciatic and Lumbar Pain, M. Clin. North America **14:** 967 (Jan.) 1931.

11. Riser, Bezy and Boularan: Tumeur de la queue de cheval et de la moëlle lombo-sacrée. Ayant évolué pendant six ans sans troubles objectifs de la sensibilité, localisée seulement par le lipiodol, Rev. neurol. **2:**673 (Nov.) 1928.

12. Hanse, A.: Erleichtert die Jodölprobe die differentialdiagnostischen Schwierigkeiten bei Conus-Caudatumoren? Arch. f. Psychiat. **82:**349 (Dec. 14) 1927.

13. Globus, J. H., and Strauss, Israel: Intraspinal Iodolography: Subarachnoid Injection of Iodized Oil as an Aid in the Detection and Localization of Lesions Compressing the Spinal Cord, Arch. Neurol. & Psychiat. **21:**1331 (June) 1929.

14. This case was previously reported by P. C. Bucy, (Blood Vessel Tumors of the Spinal Canal, S. Clin. North America **12:** 1323 [Oct.] 1932).

a slight lumbar pain that radiated down the back of the left leg as far as the knee in November, 1925. This became more severe, and two months later a physician made a diagnosis of sciatica. Six months after the onset, the pain was so severe that the patient was obliged to give up work. After seeing one physician after another, two years after the onset of the trouble a surgeon made a diagnosis of a tumor of the spinal cord and performed a laminectomy from the tenth thoracic to the second lumbar vertebra. Prior to this laminectomy a puncture in the space between the third and fourth lumbar vertebrae had revealed markedly xanthochromic fluid, containing 900 mg. of total protein per hundred cubic centimeters and no cells. Nothing was found at the laminectomy, and the pain continued. Two months later the pain began to involve both legs, and a little later the same surgeon performed a second operation, including the third and fourth lumbar laminae. Among the roots of the cauda equina was found a large tortuous artery, which was removed, but after the operation the pain was much worse. Five months before admission the patient began to take morphine and was soon taking several ¼-grain (0.016 Gm.) tablets a day. He had no trouble with the bowels or bladder except some constipation following the last operation.

Examination.—General physicial examination revealed no nevi of the skin or other abnormalities. Neurologic examination of the cranial nerves and upper extremities gave negative results. The gait was normal, except that pain rendered it difficult. There was no muscular atrophy or weakness, but there were coarse twitchings of fiber bundles in the muscles of the buttocks and back of the thighs. Frequently the muscles of the thighs and calves would contract suddenly into hard painful masses. The right patellar tendon reflex was normal, the left absent or feeble; the right achilles tendon reflex was feeble, the left either absent or feeble. The abdominal and cremasteric reflexes were normal, and Babinski's sign was negative. Sensory examination gave negative results except for some increased sensitivity to pain below the ninth dorsal segment.

Clinical Diagnosis.—The unilateral distribution of the pain in the early stages was indicative of caudal involvement, but later the pain became bilateral. The freedom from urinary and bowel disturbance was also indicative of a lesion of the cauda. On the other hand, the muscular twitchings, the absence of atrophy and the intensity of the pain and sensory changes up to the ninth dorsal segment were suggestive of a lesion of the cord higher up. Because of the uncertainty of diagnosis, resort was made to roentgen examination after the injection of iodized poppy seed oil.

Laboratory Examinations.—A cisternal puncture was made and 1.5 cc. of iodized poppy seed oil injected. Roentgenograms taken with the patient standing revealed arrest of the oil opposite the lower border of the fourth lumbar vertebra (fig. 1*A*), with many globules scattered about, doubtless arrested by adhesions from previous operations. Ordinarily, with gravity, iodized poppy seed oil will descend to the level of the second or third sacral segment, forming a cone-shaped shadow with its point downward. For purposes of comparison two examples of these sacral cones in normal cases are shown in figure 2. The cisternal fluid was clear and colorless and contained a moderate amount of globulin.

Operation.—A laminectomy was performed by Dr. Bailey on Feb. 9, 1929. The spinal canal was opened from the fourth lumbar vertebra to the middle of the sacrum. Both the bone and the dura in the sacral region were very thin. When the dura mater was opened the lower part of the dural sac was seen to be filled with a yellow gelatinous material. When this was removed, a reddish

tumor could be seen, and the roots of the cauda equina were surrounded by reddish nodules and masses of tumor. The upper margin of the tumor was at the superior border of the fifth lumbar vertebra. Attempts to remove the tumor resulted in such severe bleeding that only a small portion could be secured for microscopic study.

Postoperative Course.—It was necessary to catheterize the patient for three days following the operation. Three weeks after the operation he was able to walk, and he was discharged on March 5, 1929. When last seen, three years after the operation, he had complete control of the bladder and bowels. He had

Fig. 1.—*A* (case 1), the iodized poppy seed oil injected into the cisterna magna has descended in the subarachnoid space to the lower border of the fourth lumbar vertebra. The film was taken with the patient in the erect position, head upward. The absent spines and laminae of the third and fourth lumbar vertebrae are the result of a previous laminectomy. *B* (case 4), the iodized poppy seed oil injected into the space between the second and third lumbar vertebrae is blocked opposite the body of the fourth lumbar vertebra. The film was taken with the patient in the erect position, head upward. Partial sacralization of the fifth lumbar vertebra on the left is also to be noted.

gained 50 pounds (22.7 Kg.) and "felt fine" except for a sensation of tightness in the right buttock. He was still taking a morphine tablet once or twice a week. There was no disturbance in sensation or motor function. Both knee

jerks were diminished, and the ankle jerks were absent. During the three years following operation the patient received frequent roentgen treatments.

Pathologic Changes.—Histologic examination of the operative specimen revealed many fine capillaries with walls formed by a single layer of endothelium scattered in a dense connective tissue stroma. In one portion of the section was a large collection of closely packed cells with elongated nuclei arranged in parallel rows. The tumor was diagnosed as a hemangioma.

Comment.—In this case the early use of iodized poppy seed oil might have prevented unnecessary surgical explorations. It also represents

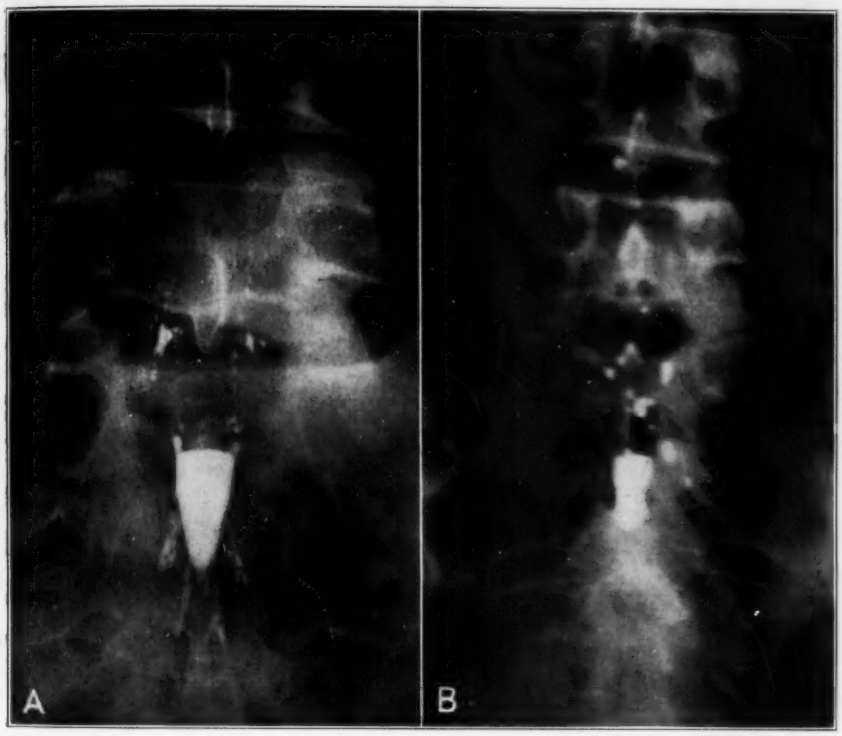

Fig. 2.—*A*, normal sacral subarachnoid sac. This picture is introduced for the sake of comparison with the block shown in figure 1. Ordinarily with gravity iodized poppy seed oil will descend to the level of the second or third sacral segment, forming a cone-shaped shadow with its point downward. The film was taken with the patient in the erect position, head upward. *B*, normal sacral subarachnoid sac. This picture shows the slight normal variation in these sacs. The film was taken with the patient in the erect position, head upward.

the type of case in which the use of this oil would be preferable to multiple spinal punctures. The extreme vascularity of the tumor might have made multiple punctures a dangerous procedure. The diagnosis of tumor of the spinal cord prior to the first operation was made prob-

able by finding xanthochromic fluid containing an excess of total protein accompanied by a normal cell count. It has been shown by Grinker [15] and others that xanthochromia may accompany conditions in the intraspinal canal other than tumor. Such a Froin syndrome is typically found below a tumor or other subarachnoid block. However, as this case illustrates and as Cushing and Ayer pointed out in a series of 5 cases, xanthochromia and increased protein may occur above tumors of the cauda equina. It is possible that a more extensive manometric study before the first operation might have revealed the absence of block above the puncture and indicated that the xanthochromia was of unusual origin. The hyperalgesia below the ninth dorsal segment might be attributed to the first operation.

CASE 2.—*Pain in the lumbar region and both legs. Partial subarachnoid block. Localization with iodized poppy seed oil. Laminectomy. Partial removal of the tumor of the conus medullaris and cauda equina. Marked improvement.*[16]

History.—J. W., a white man, aged 54, who was referred to the University of Chicago Clinics by Dr. Peter Bassoe on April 30, 1929, complained of pain in the lumbar region radiating down the legs. Two years prior to admission the pain began in the lower part of the back, but did not radiate at that time. A diagnosis of sciatica was made by a physician in another city, and the patient's teeth and tonsils were removed. Complete freedom from pain ensued until nine weeks before entrance when the pain in the back recurred, occurring mostly at night. Three weeks later the pain began to radiate down the back of the left leg and down the anterior and posterior portions of the right leg. Coughing or sneezing greatly aggravated the pain. He began to have difficulty in urinating. Five days before entrance a lumbar puncture was done elsewhere, following which the pain was much worse.

Examination.—General physical examination gave negative results except for the presence of multiple pedunculated moles. There were no neurologic evidences of abnormality in the cranial nerves of the upper extremities. Station and gait were normal, and there was no demonstrable muscular weakness. The abdominal and cremasteric reflexes were active and equal. The patellar reflexes were very weak, but equal; the achilles reflexes were more nearly normal, but the right was less active than the left. Babinski's sign was negative. Sensory examination revealed hyperesthesia over the anterior surface of both thighs, especially the right, and hypesthesia over the distribution of the fourth and fifth sacral segments in the perianal region.

Clinical Diagnosis.—The bilateral symptoms were suggestive of a conus lesion, as were the disturbances in the bladder. The severe pain and relative weakening of the patellar reflexes were indicative of involvement of the cauda. A clinical diagnosis of tumor of the upper portion of the cauda equina was made, but the uncertainty of such a diagnosis made confirmatory evidence desirable.

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15. Grinker, Roy R.: Chronic Arachno-Perineuritis with the Syndrome of Froin: Report of a Case with a Discussion of Pseudotumor. Spinalis, J. Nerv. & Ment. Dis. **64**:616 (Dec.) 1926.

16. This case was previously reported by P. Bailey, and P. C. Bucy (Tumors in the Spinal Canal, S. Clin. North America **10**:233 [April] 1930).

Laboratory Examinations.—A lumbar puncture was made in the space between the third and fourth vertebrae three days before operation. The initial pressure was 140 mm. of fluid. It rose very slowly to 170 mm. on jugular compression, falling slowly to 160 mm. when the pressure was released. After removal of 3 cc. of markedly xanthochromic fluid the pressure fell to 30 mm. At this time 1.5 cc. of iodized poppy seed oil was injected, and the patient was examined under the fluoroscope on the tilting table. With the head downward, the oil was completely arrested opposite the body of the second lumbar vertebra (fig. 3*A*). Laboratory examination revealed a spontaneously coagulating fluid, with 4 leuko-

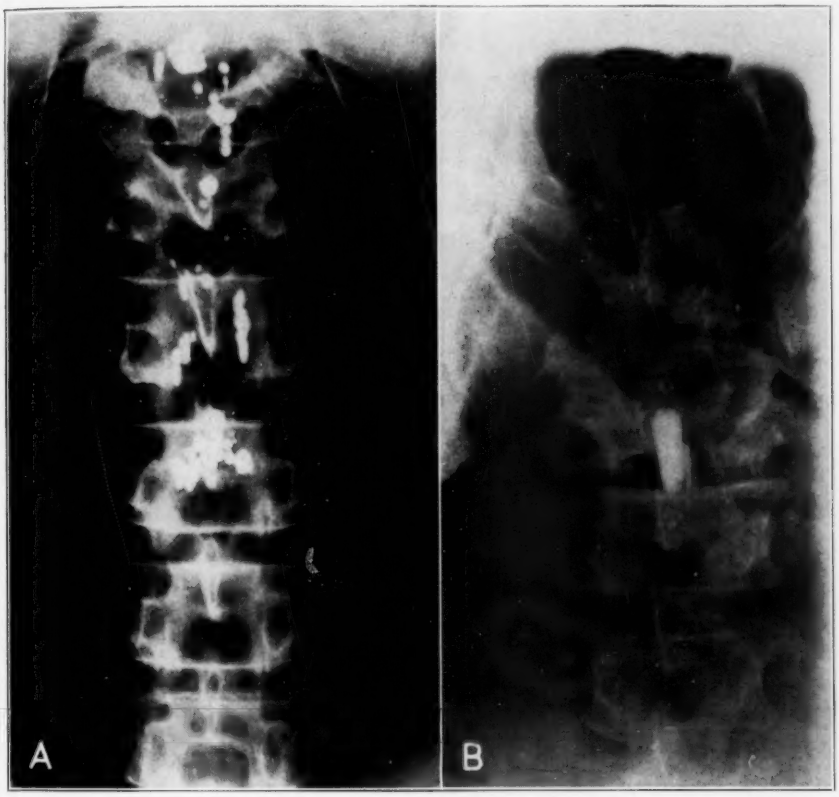

Fig. 3.—*A* (case 2), the iodized poppy seed oil injected into the space between the third and fourth lumbar vertebrae is completely arrested opposite the body of the second lumbar vertebra. The film was taken with the head downward. *B* (case 3), the iodized poppy seed oil injected into the space between the fourth and fifth lumbar vertebrae is arrested opposite the fourth lumbar vertebra. The film was taken with the head downward.

cytes per cubic centimeter, and a strongly positive test for globulin. About forty-five minutes after the puncture the patient experienced excruciating pain down the back of the right thigh.

Operation.—A laminectomy was performed by Dr. Bailey on May 4, 1929. The spines and laminae of the first to the third lumbar vertebrae were removed,

and the dura mater beneath was seen to be bulging and dark. When the dura was opened, a dark grayish-red tumor was seen lying dorsal to the roots of the cauda and extending from the conus to the lower margin of the third lumbar vertebra. The tumor was closely adherent to the nerve roots on the right side. The capsule of the tumor was incised along its dorsal surface, and the contents were removed; later, as much of the capsule was removed as possible.

Postoperative Course.—It was necessary to catheterize the patient for eleven days after operation, but otherwise convalescence was uneventful. He received roentgen therapy from May 17 to 24. When last seen, nineteen months after operation, he was entirely free from symptoms except for a little dull pain in the operative region.

Comment.—This case indicates that attempts to rule out a tumor of the cauda equina should be made before accepting the diagnosis of bilateral sciatica. The exacerbation of the pain caused by coughing, sneezing and straining at stool and after removal of lumbar fluid were all indicative of an intraspinal lesion, as were the disturbances in the bladder. It is possible that multiple lumbar punctures might have localized the site of the tumor as accurately as the injection of iodized poppy seed oil. It is to be noted that the oil localized the tumor the width of one vertebra higher than the operative finding. This may have been due to an error in counting the vertebrae or to the effect of gravity on the tumor when the oil was observed with the head down. The specimen removed at operation was lost in the pathologic laboratory, but the tumor was probably a so-called giant tumor of the cauda equina.

CASE 3.—*Pain in the lumbar region radiating down both legs. Partial subarachnoid block. Localization with iodized poppy seed oil. Laminectomy with removal of chondroma of the intervertebral disk. Recovery.*[17]

History.—H. S., a junk dealer, aged 47, who was referred to the University of Chicago Clinics by Dr. D. B. Rotman and Dr. Peter Bassoe on July 3, 1929, complained of pain in the back radiating down the posterior aspects of the legs. Three years before entrance he had had severe pain in the lower part of the back and was advised to wear a sacro-iliac belt by a physician who made a diagnosis of sacro-iliac strain. The belt relieved the pain, but in the next three years the patient had about six similar attacks of pain low down in the back, each attack subsiding a few days after the belt was worn. He was free from pain during the winter, 1928-1929, until April 25, 1929, when it recurred. The following day it was more severe, and for the first time radiated down the posterior aspects of the legs. Two days later, while lifting a heavy piece of iron, he suddenly suffered such a severe attack of pain in the back and legs that he fell to the ground and was unable to move. He was practically bedridden until two weeks before entrance, when three lumbar punctures were performed at another hospital, after which the pain became worse. At no time was there any urinary complaint, but since he had been in bed he had been somewhat constipated.

17. This case was previously reported by (*a*) P. C. Bucy, (Chondroma of Intervertebral Disk, J. A. M. A. **94**:1552 [May 17] 1930) and by (*b*) P. Bailey and P. C. Bucy.[16]

Examination.—General physical examination gave essentially negative results; there were no nevi of the skin. There were no abnormal neurologic signs in the region of distribution of the cranial nerves or in the upper extremities. Sensory examination revealed hypesthesia to painful and tactile stimuli in the lower extremities, but no definite upper level was determined although it seemed to go as high as the twelfth dorsal segment. There was no alteration of response to thermal stimuli. The patient's station was normal. The gait was very slow, and he held the legs very tense to protect himself from the extreme pain which motion elicited. There was definite weakness of the flexors of the left knee, all other muscle groups being relatively normal. Percussion of the lumbar spine produced coarse myoclonic twitchings of the muscles of the posterior aspect of the right thigh and right calf. The fourth lumbar spine was somewhat tender to pressure. Lasègue's sign was positive on the left. There was no demonstrable tenderness of the sciatic nerves. The abdominal and cremasteric reflexes were distinctly hyperactive, as were the patellar and achilles reflexes; the latter were stronger on the right than on the left. The Babinski test was negative.

Clinical Diagnosis.—The bilateral symptoms, muscular twitchings and indefinite sensory level extending up onto the abdomen were suggestive of a conus lesion. On the other hand, the severity of the pain and absence of involvement of the bladder were indicative of a caudal lesion. A clinical diagnosis of radiculomyelitis, probably of inflammatory origin, extending at least up to the twelfth dorsal segment, and probably to the eighth dorsal segment, was made.

Laboratory Examinations.—A lumbar puncture in the space between the third and fourth vertebrae yielded no fluid. This had also been the experience of Dr. Rotman and Dr. Bassoe. When the needle was introduced between the fourth and fifth lumbar spines, the initial pressure was 120 mm. of fluid. It rose very slowly on jugular compression to 300 mm., falling slowly to 180 mm. when the pressure was released. After removal of 3 cc. of clear fluid, the pressure fell to 40 mm. It rose on jugular compression to 100 mm. and then fell to 80 mm., and a few more drops of fluid were obtained. The pressure was then so low that it could not be read. At this time (two days before operation) 1.5 cc. of iodized poppy seed oil was injected and the patient examined under the fluoroscope on the tilting table. The oil descended into the sacral sac, but with the patient's head lowered it would not pass beyond the fourth lumbar vertebra (fig. 3*B*). Laboratory examination of the spinal fluid revealed 198 mg. of total protein per hundred cubic centimeters. Wassermann tests of the blood and spinal fluid were negative.

Operation.—A laminectomy was performed by Dr. Bailey on July 6, 1929. The laminae of the first to the fifth lumbar vertebrae were removed. The dura mater was opened, and it was seen that the roots of the cauda equina were injected and pushed backward at the level of the junction of the third to the fourth vertebral bodies. Above this point there was pulsation of the arachnoid and below it no pulsation. Iodized poppy seed oil escaped when the arachnoid was opened below the block. At the site of the block the roots were dislocated backward and to the left by a smooth rubbery and resistant elevation of the dura mater anterior to the cord. This protuberance arose from the intervertebral space between the bodies of the third and fourth lumbar vertebrae; it was 1 cm. long and projected 0.5 cm. into the canal. After the dura was incised, a yellowish tumor was removed in pieces with a curet.

Postoperative Course.—It was necessary to catheterize the patient for five days following operation. At the time of discharge from the hospital, eighteen

days after operation, he was entirely free from pain and was able to stand on either foot alone. Sensation was normal. The superficial reflexes were still somewhat hyperactive. Three months after operation the patient was entirely well except for very occasional pain in the back on overexertion.

Pathologic Changes.—Histologic examination of the operative specimen revealed a typical chondroma composed of fibrocartilage.

Comment.—Multiple lumbar punctures coupled with the manometric findings were of distinct aid in localizing the tumor. Iodized poppy seed oil gave confirmatory evidence as to the site of the lesion. It is possible that the frequent strain of lifting heavy weights necessitated by the patient's occupation and especially the lifting of the heavy object just before the last attack may have caused a posterior displacement or herniation of the tumor.

CASE 4.—*Pain in the lumbar region and difficult urination. Exacerbation of the symptoms following a fall. Localization of subarachnoid block with iodized poppy seed oil. Laminectomy. Removal of chondroma of the intervertebral disk. Improvement.*

History.—S. N., a white man, aged 33, on first admission to the University of Chicago Clinics, on Dec. 12, 1932, complained of increasing urinary frequency, nocturia and dysuria of at least eight years' duration. In addition, he had had intermittent attacks of dull pain low in the back for five years. Cystoscopy revealed a small ulcer of the bladder, and the patient was treated in the genito-urinary department for chronic cystitis. During the course of treatments the pain in the back became definitely worse. The pain was most severe when the patient was sitting and was referred to the left gluteal region. It was particularly severe at night and at times was made more severe by sneezing. Activity did not affect the intensity of the pain, and it never radiated down the legs at this time. An orthopedic surgeon made a diagnosis of sacro-iliac strain and advised strapping of the back with adhesive tape; this gave no relief. Examination revealed no absent or abnormal reflexes, but no sensory tests were made at this time. The residual urine as determined on one occasion was 10 cc.

On Feb. 14, 1933, when going home after an irrigation of the bladder, the patient slipped on the ice in front of the hospital and fell backward. He caught himself with his hands so that no portion of the spine touched the ground. The patient was able to walk unassisted to the hospital. He first felt severe pain in the lumbar region radiating down the legs, especially the left. Within a few minutes he noticed tingling over the sacrum and posterior aspects of both legs. This was soon followed by a feeling of numbness in these regions. On admission to the hospital the patient was unable to void, and because of considerable pain caused by distention of the bladder he had to be catheterized at frequent intervals. A retention catheter was introduced for six days, after which the patient regained some ability to void, although the amount of residual urine varied from 120 to 500 cc. The numbness in the sacral region and legs persisted, and on March 2, 1933, the patient began to complain of severe burning pain over the outer aspect of the right ankle and foot. Later, pain radiated down the posterior aspect of the thighs and calves, especially on the right.

Physical Examination.—Examination after the patient's fall on the ice revealed no abnormalities in the cranial nerves or upper extremities. The abdominal and cremasteric reflexes were present, the patellar reflexes somewhat

exaggerated, and the achilles reflexes absent. There was no clonus, and the Babinski test was negative. There was weakness of the flexors of the left knee and weakness of plantar flexion of both ankles. Beevor's sign was negative. The Lasègue and Kernig signs were positive bilaterally. Sensory examination revealed analgesia and anesthesia over the third, fourth and fifth sacral segments, the right side being more insensitive than the left. The anal skin reflex was absent. Position and vibration sense were intact. Gradually sensation over the right foot diminished, while that over the sacrum improved.

Clinical Diagnosis.—The bilateral involvement, marked urinary symptoms and sparing of the patellar reflexes were suggestive of a conus lesion. The severity of the pain was indicative of a caudal lesion. A diagnosis of possible tumor of the spinal cord was made, but no definite statement as to the localization was attempted, except that the lesion was probably in the lumbosacral canal.

Laboratory Examinations.—Lumbar puncture in the space between the third and fourth vertebrae revealed essentially normal dynamics. A lumbar puncture in the space between the second and third vertebrae, made on March 3, 1933, also revealed normal dynamic changes. At this puncture, 1.25 cc. of iodized poppy seed oil was injected into the subarachnoid space, and the patient was examined fluoroscopically on the tilting table. The opaque oil circulated freely upward, but did not descend below the body of the fourth lumbar vertebra, as seen in figure 1*B*. Sacralization of the fifth lumbar vertebra on the left was also noted. Laboratory examination of the spinal fluid removed showed no xanthochromia, a negative Wassermann reaction, a normal cell count and 50 mg. of total protein per hundred cubic centimeters.

Operation.—A laminectomy was performed by Dr. Bailey on March 4, 1933. The spinal canal was opened from the third lumbar to the second sacral segments. After opening of the dura mater it was seen that the roots of the cauda equina were bound together by adhesions opposite the fourth to the fifth lumbar interspace. Iodized poppy seed oil was present above these adhesions, and below them was an arachnoid cyst which did not communicate with the subarachnoid space above. The adhesions were loosened and the roots of the cauda displaced out of the canal. A yellowish protuberance was seen bulging from the anterior wall of the canal. This swelling was smooth and rubbery and bulged out the dura in the region of the fourth lumbar intervertebral disk. An incision was made in the dura, and a yellowish tough mass was delivered through the opening. The neck of the growth was ligated with a silver clip and a bit of muscle placed in the cavity. Some caudal roots had been caught between the bulging tumor and the right side of the canal. These were freed and replaced in the canal. After removal of all visible iodized poppy seed oil the dura and wound were closed in the usual manner.

Postoperative Course.—The pain previously present in the legs and feet entirely disappeared after operation. An inlying catheter was inserted and used for two weeks. After this was removed the patient was able to void spontaneously, and the residual urine decreased to 100 cc. Cystometric studies revealed that the tonus of the bladder was the same as before operation. Three weeks after operation the patient was discharged from the hospital. He then had no pain, except in the operative region, and was able to walk without limp, ataxia or spasticity. All muscular movements were well executed, and plantar flexion was stronger than before operation. The ankle jerks were absent and the knee jerks active. The sensory diminution was the same as before operation, except that sensation had been entirely recovered over the third, fourth and fifth sacral segments on the left side.

Pathologic Changes.—The tumor, about 4 by 2 by 2 cm. in size, was of a rubbery consistency. Histologic examination revealed a structure typical of a chondroma.

Comment.—It is probable that this chondroma had been pressing on the cauda equina for many years and that the trauma of the patient's fall caused it to herniate out even farther. At the time of operation, when the dura covering the tumor was incised the latter delivered itself through the opening as though under pressure. This patient and the patient in case 3 had chondromas arising from an intervertebral disk. This condition is not rare. Bucy,[17a] in 1930, was able to collect 16 instances of this condition, including the example in case 3, and 15 cases from the literature. Alajouanine and Petit-Dutaillis,[18] in 1930, presented 2 more instances, one in a woman, aged 20, and the other in a man, aged 37. It is interesting that this man had lumbarization of the first sacral vertebra, while the patient in case 4 of the present paper had unilateral sacralization of the fifth lumbar vertebra. These authors also saw a chondroma arising from an intervertebral disk at necropsy and cited 2 additional cases found at operation by Robineau. Cabot[19] and Kortzeborn[20] each reported a similar case. Mixter[21] stated that he had seen 7 of these cases. Elsberg,[22] in 1931, mentioned an additional case quoted in the literature and discussed 16 cases of his own, 9 of which had not been previously reported. Elsberg considered these tumors as ecchondroses. In a series of 100 laminectomies for tumor of the spinal cord he found a ventral chondroma in 14 instances. Twelve of his cases were in men and 3 in women. Nine of the tumors occurred in the cervical region, 4 in the lumbar region and 2 in the thoracic region. This cervicolumbar predilection may be because the ligamentum longitudinale posterius is less well developed in these regions or because these parts of the spine move more than the more rigid thoracic portion. Most of Elsberg's tumors protruded on one side or the other of this ligament. The so-called enchondromas arising from the vertebral bodies

18. Alajouanine, T., and Petit-Dutaillis, D.: Le nodule fibro-cartilagineux de la face postérieure des disques intervertébraux, Presse méd. **38**:1657 (Dec. 6); 1749 (Dec. 20) 1930.

19. Cabot, R. C.: Case Record Number 18222, New England J. Med. **206**:1157 (June 2) 1932.

20. Kortzeborn, A.: Schmorl'sches Knorpelknötchen unter dem Bilde eines Rückenmarkstumors im Bereich des Halsmarkes, Zentralbl. f. Chir. **57**:2418 (Sept. 27) 1930.

21. Mixter, W. J.: Spinal Column and Spinal Cord, in Lewis, Dean: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1917, vol. 12, chap. 4.

22. Elsberg, C. A.: The Extradural Ventral Chondromas (Ecchondroses), Their Favorite Sites, the Spinal Cord and Root Symptoms They Produce, and Their Surgical Treatment, Bull. Neurol. Inst., New York **1**:350 (June) 1931.

themselves, as in the case reported by Ljachovitzky,[23] are of a different origin and type. Adding my 2 cases of chondroma arising from the intervertebral disk to those previously reported in the literature, at least 40 such tumors have been reported as found at operation. In a series of 368 necropsies, Andrae [24] found these tumors in 56 instances (15.2 per cent). In the bodies of 174 men Andrae found these tumors 20 times, and in the bodies of 194 women, 36 times. These necropsy observations indicate no marked sex disproportion, while Elsberg's operative statistics indicate a marked preponderance in males. It is possible that the active life of males allows more chance of traumatic displacement of these tumors, rendering them capable of giving symptoms. Andrae's necropsy figures show the chondromas about equally distributed in different parts of the spinal column, while Elsberg's operative series shows a cervicolumbar predilection. This may also be explained by the action of trauma in the cases in which operation is necessary.

LIMITATIONS OF THE USE OF IODIZED POPPY SEED OIL

Following the introduction of iodized poppy seed oil by Sicard and Forestier as a medium for the visualization of the epidural space,[25] in 1921, and of the subarachnoid space,[26] in 1922, the use of this substance has become widespread. Sicard and Forestier published a book [27] on the varied uses of iodized poppy seed oil in 1928, and other reports [28] of these authors have been very favorable. However, not all observers have found the subarachnoid use of this substance entirely safe. Reports of its toxicity indicate that it should not be used indiscriminately. Furthermore, iodized poppy seed oil does not always help in localizing an intraspinal lesion. Christophe [29] reported 2 cases in which the oil showed a complete block in the dorsal region, but operation gave entirely nega-

23. Ljachovitzky, M. M.: Enchondrom der Wirbelsäule, Deutsche Ztschr. f. Chir. **224**:319 (June) 1930.

24. Andrae, R.: Ueber Knorpelknötchen am hinteren Ende der Wirbelbandscheiben im Bereich des Spinalkanals, Beitr. z. path. Anat. u. z. allg. Path. **82**:464, 1929.

25. Sicard, J. A., and Forestier, J.: Méthode radiographique d'exploration de la cavité épidurale par le lipiodol, Rev. neurol. **37**:1264, 1921.

26. Sicard, J. A., and Forestier, J.: Méthode générale d'exploration radiologique par l'huile iodée (lipiodol), Bull. et mém. Soc. méd. d. hôp. de Paris **46**: 463 (March 17) 1922.

27. Sicard, J. A., and Forestier, J.: Diagnostic et thérapeutique par le lipiodol, Paris, Masson & Cie, 1928, p. 1.

28. Sicard, J. A., and Laplane, L.: Diagnostic des tumeurs rachidiennes forme pseudo-pottique—radio-lipiodol, Presse Méd. **33**:33 (Jan. 10) 1925.

29. Christophe, L.: Sur le valeur diagnostique d'un arrêt du lipiodol intrarachidien, Rev. neurol. **2**:490, 1927.

tive results. De Martel [30] stated that iodized poppy seed oil is seldom necessary and that he did not believe the surgical treatment of the spinal cord has been much modified by its use. Nonne [31] also concluded that this substance should be used only in certain cases. Bregman and Szpilman [32] reported 6 cases in which iodized poppy seed oil gave misleading information.

Clinical Evidence of the Toxicity of Iodized Poppy Seed Oil.—Frequent references are made in the literature to the toxic effects of iodized poppy seed oil. Armour [33] found that after the intraspinal use of this oil there is often an increase in root pains, general soreness, stiffness of the muscles of the back, headache and fever. He noticed a distinct meningeal reaction in patients submitted to operation shortly after the injection of iodized poppy seed oil. Mackeddie [34] used the oil in 12 cases and concluded that it may temporarily irritate abnormal nerve tissue but not healthy nerve tissue. This author did not state the indications for its use when only healthy nerve tissue is present. Maclaire,[35] and later Sharpe and Peterson,[36] removed iodized poppy seed oil at a second operation in cases in which they believed the intraspinal damage was definitely increased by the oil. Lindblom [37] used this substance in 5 cases and found that all of the patients had pronounced meningeal symptoms and a pleocytosis as high as 1,000 white cells per cubic millimeter. Craig,[38] in presenting 5 cases as illustrations of the use of iodized poppy seed oil and 5 others as illustrations of its abuse, found that it is apt to produce a meningeal reaction and exacerbation of the symptoms. Ebaugh and Mella [39] injected iodized poppy seed oil by

30. de Martel, T.: Lipiodol in Spinal Cord Surgery, Rev. neurol. **1**:496, 1927.

31. Nonne, M.: Kritische Bemerkungen zur Jodipin-Diagnostik bei Rückenmarkserkrankungen, Deutsche Ztschr. f. Nervenh. **102**:6 (Jan.) 1928.

32. Bregman, L. E., and Szpilman, P.: Zur Lipjodoldiagnose bei Rückenmarkskrankheiten, Deutsche Ztschr. f. Nervenh. **103**:302 (May) 1928.

33. Armour, D.: Surgery of the Spinal Cord and Its Membranes, Lancet **1**: 423 (Feb. 26) 1927.

34. Mackeddie, J. F.: Lipiodol Injections as a Diagnostic Agent, M. J. Australia **1**:577 (May 22) 1926.

35. Maclaire, A. S.: Lipiodol in Neurosurgery, with a Report of a Case with Deleterious Results, Am. J. M. Sc. **170**:874 (Dec.) 1925.

36. Sharpe, W., and Peterson, C. A.: The Danger in the Use of Lipiodol in the Diagnosis of Obstructive Lesions of the Spinal Canal, Ann. Surg. **83**:32 (Jan.) 1926.

37. Lindblom, A. F.: On the Effect of Lipiodol on the Meninges, Acta radiol. **5**:129, 1926.

38. Craig, W. M.: The Use and Abuse of Iodized Oil in the Diagnosis of Lesions of the Spinal Cord, Surg., Gynec. & Obst. **49**:17 (July) 1929.

39. Ebaugh, F. G., and Mella, H.: The Use of Lipiodol in the Localization of Spinal Lesions: II. The Local and Systemic Effects of the Injection of Lipiodol into the Subarachnoid Space, Am. J. M. Sc. **172**:117, 1926.

cisternal puncture into 13 patients, and noticed that spinal punctures made afterward were often bloody. They found, however, no evidence of permanent ill effects. Stölzner [40] presented the case of a man, aged 47, in whom impotence developed after the use of iodized poppy seed oil. Thurzó [41] found slight secondary reactions following iodolography. Wolfsohn and Morrissey [42] stated that in two laminectomies after iodolography, inflammatory changes were found around the tumor. The toxicity of iodized poppy seed oil is discussed in a recent report of the Council on Pharmacy and Chemistry of the American Medical Association.[43]

These clinical reports indicate that iodized poppy seed oil is somewhat irritant. It seems definitely established that after the use of this oil there may be headache, nausea, pain in the back and an increase in the spinal fluid cell count. However, it must be remembered that many of the bad results attributed to the oil may have been due to the primary lesion or to the operative trauma. Some of the immediate ill effects and the exacerbation of symptoms may have been due to the removal of fluid from below the tumor. The symptoms also may have been confused with the usual postpuncture headaches.

Not all reports in the literature indicate that iodized poppy seed oil is very toxic. Globus and Strauss [13] discussed the use of iodized oil by cisternal injection in 90 patients. In this entire series only 1 patient presented signs of meningeal irritation, and in this case it was very transient. In 25 patients examined roentgenologically after two years, iodized poppy seed oil was present, but freely movable. A necropsy was performed in one case three and half months after iodolography, and no evidence of meningeal irritation was found. However, in the discussion of Globus and Strauss' paper, Elsberg stated that he thoroughly believed that iodized poppy seed oil is an irritant and that he had seen fresh adhesions and marked congestion of the meninges in a number of instances. The recognition of the freshness of adhesions at operation seems difficult, and congestion of the meninges is frequent near tumors. Moll [44] concluded that the use of iodized poppy seed oil

40. Stölzner, H.: Ist die Myelographie mit Jodipin unbedenklich? Zentralbl. f. Chir. **54**:3274 (Dec. 17) 1927.

41. Thurzó, E.: Myelography with Lipiodol, Folia neuropath. estoniana **11**: 157, 1931.

42. Wolfsohn, J. M., and Morrissey, E. J.: On the Value of Lipiodol as an Aid in Neurologic Localization, California & West. Med. **26**:55 (Jan.) 1927.

43. Report of Council on Pharmacy and Chemistry: Dangers of the Injections of Iodized Oils, J. A. M. A. **99**:1946 (Dec. 3) 1932. Current Comment: Hazards of Iodized Oil Injections, ibid. **100**:46 (Jan. 7) 1933.

44. Moll, H. H.: Observations on the Diagnosis of Spinal Block by Means of Lipiodol, J. Neurol. & Psychopath. **13**:14 (July) 1932.

is a safe procedure, and Doughty [45] found no sign of meningeal irritation in 2 cases in which operation was performed after iodolography.

Experimental Evidence of the Toxicity of Iodized Poppy Seed Oil.—Davis, Haven and Stone [46] inserted rubber drains extradurally in a series of dogs to produce a subarachnoid block before injecting iodized poppy seed oil by cisternal puncture. Eight of 10 dogs that received the oil showed definite clinical evidences of irritation. The dogs were killed at intervals of from three to two hundred and fifty-two days after injection. In all the dogs definite evidences of leptomeningeal reaction, fat encystment and degenerative changes in the gray matter were found. The authors made no mention of the findings in the control dogs which received no iodized poppy seed oil. These authors also quoted Bergerhoff [47] as having to remove iodized poppy seed oil at a second laminectomy, whereas in Bergerhoff's case no laminectomy was performed.

Ayer and Mixter [48] injected iodized sesame oil 40 per cent, which is somewhat similar to iodized poppy seed oil, into cats by cisternal puncture. One cat died, and the other 5 had a pleocytosis rising as high as 4,000 white cells per cubic millimeter. The dose of from 1 to 1.5 cc. in these cats is relatively greater than is usually used in patients. Peiper and Klose [49] found that iodized vegetable oil caused chromatolysis and degeneration of the nerve cells of the cord in rabbits. Bruskin and Propper [50] injected iodized vegetable oil into 14 dogs; in 10 into the subarachnoid space, in 2 into the cord substance and into 2 controls. No symptoms were noted, but definite pathologic changes were found, including a distinct proliferative reaction about the oil droplets.

Lindblom [51] injected iodized poppy seed oil into the subarachnoid space of 7 rabbits. One rabbit died and the others were killed at

45. Doughty, R. G.: The Intraspinal Use of Lipiodol, Ann. Surg. **89**:635 (April) 1929.

46. Davis, Loyal; Haven, H. A., and Stone, T. T.: The Effect of Injections of Iodized Oil in the Spinal Subarachnoid Space, J. A. M. A. **94**:772 (March 15) 1930.

47. Bergerhoff, M.: Spätschädigung durch Jodipin, Fortschr. a. d. Geb. d. Röntgenstrahlen **36**:374, 1928.

48. Ayer, J. B., and Mixter, W. J.: Radiography Following the Injection of Iodipin Into the Spinal Subarachnoid Space, Arch. Neurol. & Psychiat. **11**:499 (April) 1924.

49. Peiper, H., and Klose, H.: Ueber die Grundlagen einer Myelographie (Klinik, Histologie, Röntgenologie), Arch. f. klin. Chir. **134**:303, 1925.

50. Bruskin, J., and Propper, N.: Experimentelle Myelo-Encephalographie an Hunden und über den Einfluss von Jodipin und Lipojodol auf das Rückenmark, Gehirn und dessen Häute, Ztschr. f. d. ges. exper. Med. **75**:34, 1931.

51. Lindblom, A. F.: On the Effects of Various Iodized Oils on the Meninges, Acta med. Scandinav. **76**:395, 1931.

intervals of from two days to four months. Signs of leptomeningitis were found in those killed early, but after a few weeks, despite the presence of iodized poppy seed oil, there were very few such signs.

Other Iodized Oils and Methods of Visualizing the Spinal Subarachnoid Space.—Dandy [52] discussed spinal visualization after the injection of air in 9 cases. Arnell and Lidström [53] injected 14 cc. of a 20 per cent solution of skiodan by lumbar puncture in 1 case; the skiodan caused no apparent ill results, gave good visualization and was absorbed in thirty minutes. Radovici and Meller [54] found that thorotrast, a colloidal solution of thorium dioxide, gives very indistinct pictures in the lumbosacral region. Saiz and Gortan [55] concluded, from the results in 18 patients, that the epidural use of iodized poppy seed oil gives misleading information.

Bruskin and Propper [50] found that the so-called ascending iodized poppy seed oil caused definite symptoms of depression and cachexia in 5 dogs. Histologic examination showed irritative changes and endarteritis obliterans of the pial vessels. These authors concluded: "Ascending iodized poppy seed oil must be completely eliminated both as a therapeutic and as a diagnostic medium from surgical and neurologic practice." Sgalitzer [56] also found that ascending iodized poppy seed oil is more irritant than the descending or common variety.

Various attempts have been made to produce iodized oils that are less toxic than iodized poppy seed oil. Frazier and Glaser [57] found that iodized rape-seed oil is relatively nontoxic, but that it produces some pleocytosis. Lindblom [51] found in experiments on rabbits that iodized vegetable and animal oils act differently. The acidity is very important, as is the presence of products of hydrolysis, such as hydrogen iodide. Sesame and soy oil produced no reaction and contained practically no free fatty acid. The poppy oil in iodized poppy seed oil contains much free fatty acid and is quite irritant. Animal oils emulsify in a few hours and are rapidly absorbed, producing an extreme meningeal reaction and death, probably by their decomposition products. Odin, Runström and

52. Dandy, W. E.: The Diagnosis and Localization of Spinal Cord Tumors, Ann. Surg. **81**:223 (Jan.) 1925.

53. Arnell, S., and Lidström, F.: Myelography with Skiodan (Abrodil), Acta radiol. **12**:287, 1931.

54. Radovici, A., and Meller, O.: Encéphalographie liquidienne par le thorotrast sous-arachnoïdien, Rev. neurol. **1**:479, 1932.

55. Saiz, G., and Gortan, M.: Die Erforschung des epiduralen Raumes durch Lipjodol, Ztschr. f. d. ges. Neurol. u. Psychiat. **115**:108, 1928.

56. Sgalitzer, M.: Myelographie mit sinkendem und aufsteigendem Jodöl, Acta radiol. **9**:136, 1928.

57. Frazier, C. H., and Glaser, M. A.: Iodized Rape-Seed Oil (Campiodol) for Cerebrospinal Visualization, J. A. M. A. **91**:1609 (Nov. 24) 1928.

Lindblom,[58] in an extensive monograph, discussed the irritant effects of iodized poppy seed oil. These authors stated that in the rabbit, sesame oil and soy oil produced no meningeal symptoms and the pia showed a normal postmortem appearance. These two oils were used in 24 patients with very good results.

From the numerous reports as to the toxicity of iodized poppy seed oil, the query might be raised as to whether this oil should ever be used in the spinal subarachnoid space. In the cervical and dorsal regions, where the nerve roots leave the spinal canal near their point of origin from the cord, tumors can usually be diagnosed sufficiently accurately from neurologic and manometric tests alone. Elsberg [59] has shown, however, that even in these regions the sensory level may rise to the true level of the tumor only late in the course of the disease. He has shown also that the more ventral the compression, the more discrepancy between the upper level of sensory disturbance and the segment actually involved. In general, however, tumors in the upper part of the cord can be diagnosed without the use of iodized poppy seed oil.

In tumors of the region of the conus medullaris and cauda equina, on the other hand, the nerve roots travel a long distance before leaving the spinal canal. Here neurologic localizing signs are less definite, and it is in these cases that iodized poppy seed oil has its chief field of usefulness. Iodized poppy seed oil is of value not only in diagnosing the presence of a block, but also, what is equally important, in determining the site of the lesion. From the surgical standpoint the latter is of prime importance. The added trauma of a long and possibly exploratory laminectomy is more to be avoided than the slight toxic effects of iodolography. In the 4 cases presented in this paper, different phases of the value of iodolography in this region were brought out. Moreover, in none of these cases was there direct evidence that the iodized poppy seed oil was injurious.

SUMMARY

A study of 4 cases confirms the general impression that the diagnosis of a tumor in the region of the cauda equina is difficult. From the surgical standpoint it is important to determine the level of such a tumor. Without a fairly accurate diagnosis of the level, an extensive laminectomy may be necessary before the tumor is found. In this region the nerve roots run for a long distance before leaving the spinal canal, and it is difficult to determine clinically the exact point of com-

58. Odin, M.; Runström, G., and Lindblom, A.: Iodized Oils as an Aid to the Diagnosis of Lesions of the Spinal Cord and a Contribution to the Knowledge of Adhesive Circumscribed Meningitis, Acta radiol. (supp.) **7**:1, 1928.

59. Elsberg, C. A.: The False Localizing Signs of Spinal Cord Tumor, Arch. Neurol. & Psychiat. **5**:64 (Jan.) 1921.

pression. Much stress has commonly been laid on the difference in the symptoms when the lesion is high enough to involve the conus medullaris, but in actual experience these differences have proved to be of little practical value. Three of the cases represent lesions of the cauda equina and the fourth a lesion of the conus medullaris. Several of the symptoms and signs commonly attributed to conus lesions were present in the cases of caudal tumor, and vice versa. Muscular twitchings are ordinarily considered to be an accompaniment of conus lesions, but were present in 2 of the cases of caudal tumors and not in the case of conus tumor. Bilateral symptoms are supposed to indicate a conus lesion, but in the 3 cases of caudal tumor the symptoms were bilateral. Early and severe symptoms of the bladder are said to be indicative of a conus lesion, but 1 of the patients with a caudal tumor had extreme urinary difficulty. A study these 4 cases thus seems to confirm the general impression that the clinical signs of differentiation between tumors of the conus and cauda are misleading.

Mechanical procedures, including a complete manometric study and iodolography, may be used to confirm the clinical diagnosis and aid in localizing the level of the lesion. A study of the literature indicates that iodized poppy seed oil is definitely toxic, although in many instances the degree of this toxicity is overestimated. Certain of the experiments on the toxicity of iodized poppy seed oil are poorly controlled, and some of the clinical reports do not differentiate accurately between the course of the primary disease and the effects of operation or removal of spinal fluid, on the one hand, and the direct effects of iodized poppy seed oil, on the other hand. It seems, however, that this oil is irritant and should be used only when other methods prove inadequate for diagnosis. In tumors of the cervical and dorsal regions, where clinical localizing signs are usually adequate, the use of iodized poppy seed oil does not seem justified. In tumors of the lumbosacral region, on the other hand, clinical differentiation and localization have proved inadequate and the use of iodized poppy seed oil seems justified.

CONCLUSIONS

1. Clinical localizing signs often prove inadequate to differentiate accurately and localize tumors of the conus medullaris and cauda equina.

2. Reports of a mild irritant action of iodized poppy seed oil seem sufficiently well founded to make one hesitate to resort to its use except when it is impossible to arrive at a diagnosis by other means. The difficulty of determining accurately the level of a tumor in the lumbosacral canal would seem to justify its use in such cases.

PROGRESSIVE NECROSIS OF THE SPINAL CORD

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The work of Oppenheim [1] and of Henneberg [2] in rewriting the chapter on myelitis was a welcome, although not an unopposed, forward step in the understanding of diseases of the spinal cord. Today the terrain of myelitis, although more sharply limited, still requires study to determine the grouping of various clinicopathologic syndromes which have been described under various headings. In this study we are concerned with what appears to be an entity that is best described under the heading of progressive necrosis of the spinal cord. The term myelomalacia has been employed to describe this condition by Schmitt [3] and others. This term would be desirable, but, owing to its usage since the time of Westphal [4] in 1874 in association with softening secondary to vascular lesions, it can scarcely be employed in this connection without causing added confusion.

Progressive necrosis of the spinal cord may appear to be of spontaneous origin, but more frequently it seems to follow closely some infectious or toxic process that is not primarly related to the central nervous system. The onset is fairly sudden; the progress is rather rapid, and the course is febrile and usually of an ascending character. Motor and sensory paralysis, with loss of sphincteric control of the bowel and bladder and extension upward toward the medulla oblongata, is present. As a rule, death is due to decubitus and secondary infection before the process has involved the cranial nerves or brain to any appreciable extent and usually before regressive changes have occurred.

From the Sections on Neurology (Dr. Moersch) and Pathologic Anatomy (Dr. Kernohan), the Mayo Clinic.

Read before the Fifty-Ninth Annual Meeting of the American Neurological Association, Washington, D. C., May 10, 1933.

1. Oppenheim, H.: Zum Capitel der Myelitis, Berl. klin. Wchnschr. **28:** 761, 1891; Lehrbuch der Nervenkrankheiten, ed. 7, Berlin, S. Karger, 1923, p. 447.

2. Henneberg, R.: Die Myelitis und die myelitischen Strangerkrankungen, in Lewandowsky, M.: Handbuch der Neurologie, Berlin, Julius Springer, 1911, vol. 2, p. 694.

3. Schmitt, W.: Ueber akute Rückenmarkserweichung (Myelomalacie), Deutsche Ztschr. f. Nervenh. **72:** 78 (Jan.) 1921.

4. Westphal, C.: Beobachtungen und Untersuchungen über die Krankheiten des centralen Nervensystems, Arch. f. Psychiat. **4:**335, 1874.

Examination of the spinal fluid, as a rule, discloses a moderately increased cell count, with an excess of total protein. The duration of the disease varies from several days to about six months. The average duration is about six weeks. The disease may, however, have a more chronic course. The pathologic picture is characterized by marked extensive necrosis, especially of the central white matter, without any inflammatory reaction or vascular lesion. As the following three cases are examples of this condition, rather detailed reports are given.

REPORT OF CASES

CASE 1.—A man, aged 37, had had occasional mild attacks of lumbar pain for six years before we saw him. At times he had a feeling as if a tight rope was around the lower part of the abdomen. On Aug. 25, 1929, seven days before examination at the clinic, he noted a feeling of tightness in the muscles of the calf. The next day he had to stop work because of pain in the legs and numbness below the knees. On the following days he was unable to move the legs, and the bowel and bladder were incontinent.

On September 2, the temperature was 99 F., and leukocytes numbered 17,400 in each cubic millimeter of blood. There was complete motor and sensory paralysis up to the level of the twelfth thoracic segment. The deep reflexes of the legs were absent, and there was no plantar extensor response. The hypogastric reflexes were absent, whereas the midabdominal and epigastric reflexes were present. Examination of the ocular fundi gave negative results. Examination of the spinal fluid disclosed many erythrocytes, and the smear for organisms was negative. In the following six days anesthesia ascended to the nipple line on the left and to the seventh rib on the right. A second examination of the spinal fluid on this day resulted in a negative reaction to the Wassermann (Kolmer) test, a determination of 60 mg. of total protein in each 100 cc. of fluid, a positive reaction to the globulin test and 165 lymphocytes and 59 polymorphonuclear leukocytes to each cubic millimeter. The colloidal gold curve was 0000112000. The spinal fluid was slightly yellow, and the response in intraspinal pressure to pressure on the jugular veins was somewhat delayed. The temperature gradually increased to 104 F., and on September 20 decubitus and pyelitis developed. The value for urea rose to 242 mg. in each 100 cc. of blood, and on September 28 the patient died, having been ill five weeks.

Necropsy.—Two decubitus ulcers were found. The muscles of the legs were markedly atrophied. No lesion was present in the peritoneal, pleural or pericardial cavities or in the organs in these cavities. There was hemorrhagic cysto-ureteropyelonephritis, with numerous miliary abscesses. In the aorta there was only very mild arteriosclerosis, graded 1; the ostia of all the intercostal arteries were patent, and arteriosclerosis was not present in these smaller vessels. Of the tissues of the central nervous system, it was possible to obtain only the spinal cord from the level of the third thoracic segment to the cauda equina. The lumbar segments of the spinal cord were soft, whereas the thoracic portion was firmer. Exudate or inflammatory reactions were not present in the subarachnoid space. The blood vessels were normal; dilatation, sclerosis and thromboses were absent. The spinal cord was cut by transverse sections. There was complete necrosis of the lower part of the lumbar portion of the cord. It was not possible to distinguish the

gray from the white substance, and the normal markings were completely obliterated. This part of the spinal cord was pultaceous. At the level of the first lumbar segment the necrosis was limited to the posterior half of the cord, although the anterior half was softer than normal. At the level of the eleventh thoracic segment the necrosis was limited to an elliptic focus at the base of the left posterior horn. From this level upward a small cavity was present in the same situation, which simulated a syringomyelic cavity but without the surrounding zone of gliosis; it contained débris similar to the necrotic zone in the lumbar region.

Histologic study of the cross-sections of the spinal cord was carried out on sections stained by as many methods as possible after fixation in formaldehyde. At the level of the fifth lumbar segment a slight excess of connective tissue in the meninges was noted, and the trabeculae of the subarachnoid space were thickened. Acute inflammation was not present, but there were several small collections of lymphocytes, especially near some of the blood vessels of medium size. There were some compound granular corpuscles (scavenger cells) with small nuclei and large, clear, vacuolated cytoplasm, which reacted for fat with specific stains. The pia mater was ruptured in several places, especially near the entrance of the posterior nerve roots, and there was herniation of the substance of the spinal cord into the subarachnoid space. The content of the hernia was identical with the adjacent substance of the cord. The posterior nerve roots showed early signs of degeneration with the Marchi stain, and the walls of the blood vessels in these roots were thickened, but the lumens were not occluded. The anterior nerve roots disclosed definite degeneration; the myelin sheaths were swollen, beaded and fragmented, and the axis-cylinders were fragmented, swollen and nodular. It was impossible to recognize the normal rounded myelin sheaths, although the white matter stained diffusely with the Weigert myelin sheath, the Mallory-Heidenhain and the Jakob-Mallory stains. There was little vacuolation of the myelin sheaths, but disintegration was universal. The gray matter also had been completely disorganized and partly disintegrated; the ganglion cells of the anterior horns were degenerating; only faint shadows could be recognized, and the Nissl granules had disappeared. The entire gray matter stained diffusely and in a manner similar to the white matter. There were no hemorrhages in the spinal cord and no acute or chronic inflammation. Scavenger cells were present only beneath the pia mater and around some blood vessels, but they had not penetrated deeply into the necrotic cord, in the center of which there was complete absence of all reaction. The glia cells had also disintegrated, and there was no attempt at proliferation or gliosis. There was no excess of connective tissue. The walls of the larger arteries were slightly thickened, especially the media, which in some seemed to have undergone a hyaline change. The smallest arteries and the arterioles had thickened walls and narrow lumens; the thickening was limited almost entirely to hypertrophy of the media, although in some vessels there was slight proliferation of the lining endothelium. There was no thrombosis of any of the vessels, and the veins were normal. There were edema of the walls and separation of the adventitia from the media, but cellular elements did not fill these spaces.

At the level of the first lumbar segment the leptomeninges were slightly thickened and fibrotic, and the two layers were fused in places. In several places there were minute hernias. The posterior nerve roots showed slight early degeneration with the Marchi stain; this was more marked in the anterior nerve roots. The walls of the larger blood vessels were normal, but there was slight thickening of the walls of most of the smaller arteries and arterioles, the lumens of which

were narrowed but not occluded. In the posterior columns, the posterior horns and the posterior halves of the lateral columns (fig. 1*A*) there was complete necrosis, with replacement by myelin débris. Scavenger cells had infiltrated into this area and had partly phagocytosed the material. The myelin nearest the gray

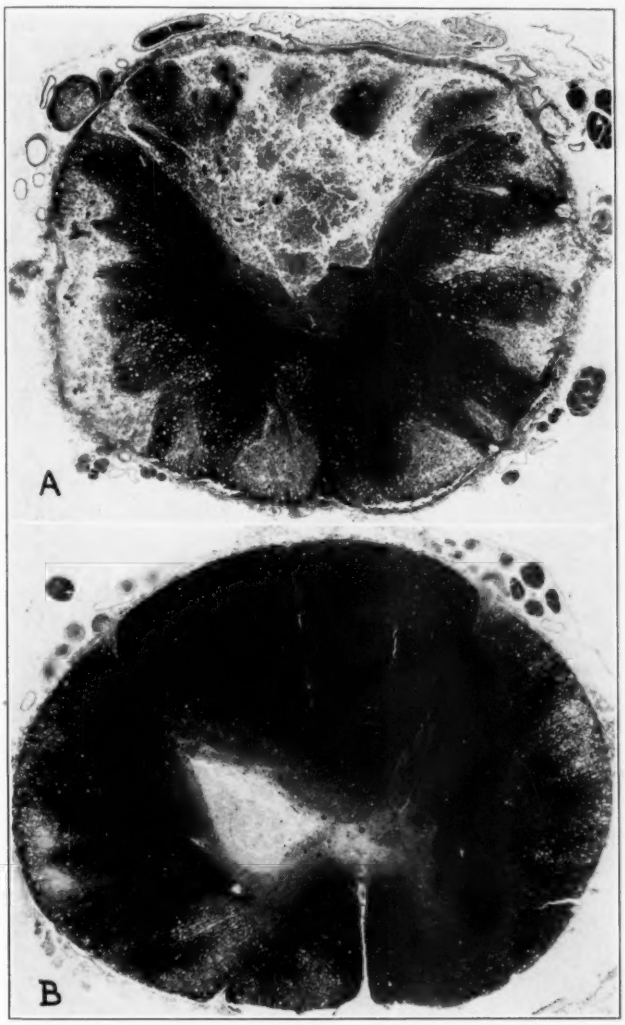

Fig. 1.—Cross-sections of a spinal cord in progressive necrosis. *A* shows necrosis of the posterior columns and lateral portions of the lateral columns. The other areas of degeneration are not necrotic but are due to secondary degeneration. The gray matter is better preserved than the white matter. *B*, an elliptic region of necrosis at the base of the posterior horn, filled with débris and scavenger cells. Weigert myelin sheath stain; × 9.

matter was better preserved than elsewhere. In the anterior half of the cord the myelin was degenerating but was not necrotic, except for one small focus between

the left anterior horn and the pia mater, where a large group of scavenger cells had replaced the myelin sheaths. In the other parts of the anterior columns and anterior parts of the lateral columns scavenger cells were present in the perivascular spaces, but the anterior horns were easily recognized; the ganglion cells were present but were undergoing chromatolysis and were swollen, and some were almost completely disintegrated. The central canal was patent but not dilated and did not contain any cellular débris. There was no gliosis or glial proliferation in any place; the glia cells had degenerated in the necrotic portions but showed no evidence of proliferation in the intact portions. The blood vessels of the spinal cord were normal. The adventitia seemed to be edematous and in places was widely separated from the media. This space contained many scavenger cells but was not completely filled with them. Inflammatory and connective tissue reactions were absent.

At the level of the eleventh thoracic segment there was complete absence of acute inflammation or other reaction in the meninges. The nerve roots and blood vessels were normal. In the spinal cord there was an elliptic area of necrosis at the base of the left posterior horn (fig. 1*B*). In this cavity there were many scavenger cells but no surrounding gliosis or proliferation of connective tissue, and the small blood vessels in the surrounding tissue were dilated and congested. Between the anterior horn and the pia mater on the left side there was a small focus of necrosis containing many scavenger cells, and also on the left side, between the pyramidal tract and the pia mater, there was another zone of necrosis with numerous scavenger cells. There was some degeneration of the myelin sheaths in the parts of the spinal cord not involved in the necrosis, but this was similar to the severe degeneration seen in combined sclerosis (associated with pernicious anemia). The posterior columns appeared to be normal, except with the Marchi stain, which disclosed evidence of extensive degeneration. There was no gliosis, but some astrocytes were swollen and degenerated. Some of the ganglion cells of the anterior horns were undergoing chromatolysis, but there was no inflammation. The central canal was patent but had a very narrow lumen.

The focus of degeneration continued upward to the level of the seventh thoracic segment, the changes continuing as those seen at the eleventh thoracic segment, only less marked. There was no glial proliferation at this level, and the glia cells which were present appeared normal. The central canal was obliterated. There was no apparent degeneration of the myelin sheaths and axis-cylinders with the general and the myelin sheath stains, but with the Marchi stain there was diffuse degeneration of the myelin in the ascending fiber tracts.

At the level of the third thoracic segment there were changes almost identical with those observed at the level of the eleventh thoracic segment. The region of necrosis at the base of the left posterior horn was larger than that seen at the level of the eleventh thoracic segment. There was another, but much smaller, region of necrosis in the left pyramidal tract; this contained numerous scavenger cells. There was no necrosis in the right pyramidal tract, but there was some degeneration of myelin here which had a spongy appearance. The Marchi stain disclosed extensive degeneration throughout the entire spinal cord, but in the posterior columns a wedge-shaped area in the center gave the reaction much more profoundly than the lateral halves of this column.

Longitudinal sections through the softened part of the lumbar portion of the spinal cord confirmed the findings seen on cross-section. The walls of the smallest arteries were thickened, and the lumens were narrowed but patent. The larger

vessels were normal. The leptomeninges were slightly fibrosed and thickened, and there were some small ruptures of the pia mater, through which the necrotic substance of the spinal cord had been extruded. The substance of the spinal cord was completely necrotic, with scavenger cells massed beneath the pia mater and adjacent to some of the larger vessels. The cord stained a diffuse blue with Weigert's myelin sheath stain. Many of the scavenger cells stained blue and were seen to contain undegenerated masses of myelin. When a modification of the Orlandi silver impregnation method was used and the material was counterstained with eosin, it was seen that all the axis-cylinders were broken into fragments, but little beading or evidence of degeneration was seen in the

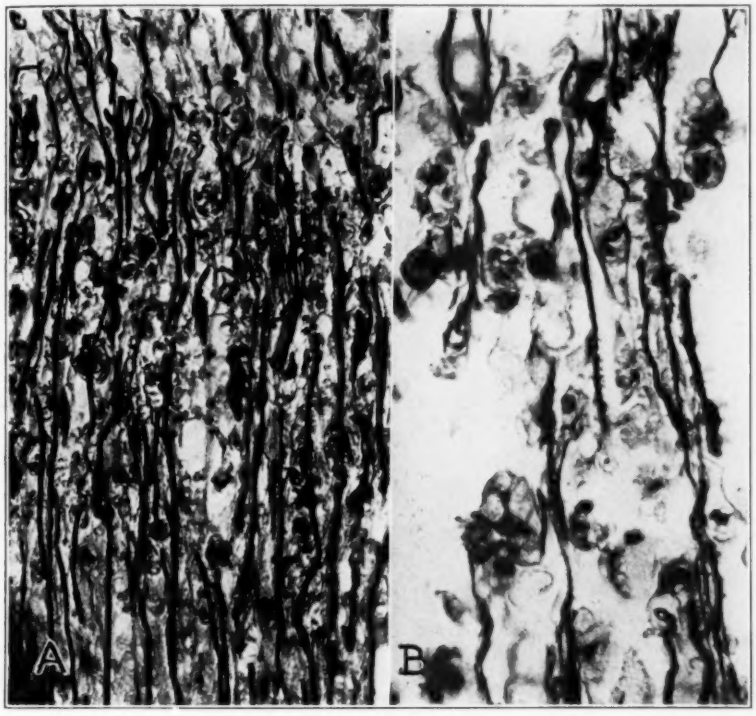

Fig. 2.—Longitudinal sections of the same spinal cord as in figure 1. In *A* the axis-cylinders are irregular in outline, swollen, beaded and fragmented. This is an early stage of degeneration. The myelin sheaths are more extensively destroyed than the axis-cylinders (modified Orlandi silver impregnation method; × 325). *B*, fragmented axis-cylinders with scavenger cells containing phagocytosed fragments of axis-cylinders (modified Orlandi silver impregnation method; × 350).

destructive lesions of the axis-cylinders. Some undegenerated fragments were seen to have been phagocytosed as small particles in scavenger cells. There was no inflammatory reaction, and there was no increase in connective tissue. The astrocytes had completely degenerated and disappeared. The ganglion cells were swollen and degenerating, and the Nissl granules also had disappeared.

Longitudinal sections through the lower thoracic portion of the spinal cord disclosed changes similar to those observed in the cross-sections. Beneath the pia mater there was a region of necrosis which was completely infiltrated with scavenger cells. In the center of the spinal cord there was a region of necrosis which was only partly infiltrated with scavenger cells. There were many small scattered regions of necrosis at the lower ends of these sections, but they diminished in size and number at the upper end. All these regions had been infiltrated and almost completely replaced by scavenger cells. Many of the myelin sheaths at the edges of these necrotic portions were undergoing degeneration; they were swollen, globular and partly fragmented. The axis-cylinders were better preserved,

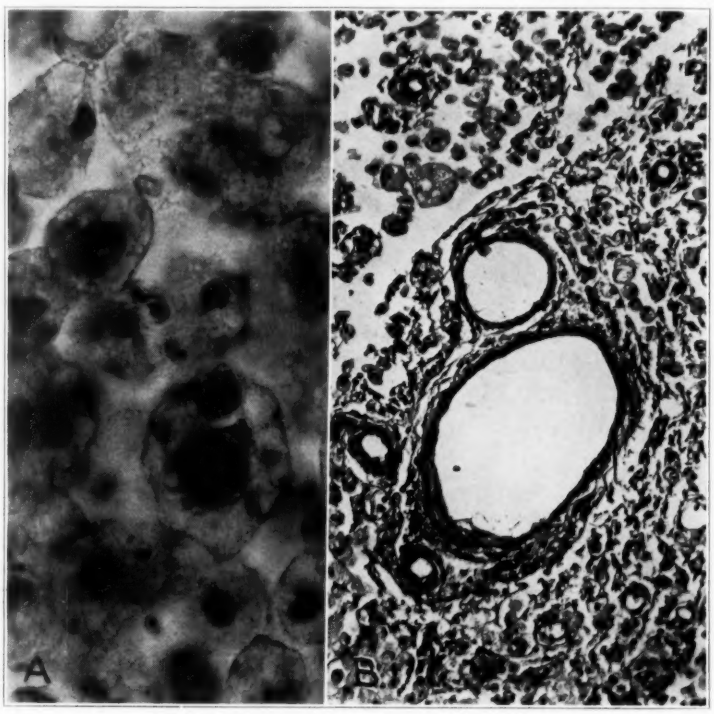

Fig. 3.—Photomicrographs of central sections of the spinal cord. In *A* one scavenger cell contains a large particle of phagocytosed but undegenerated myelin (Weigert myelin sheath stain; × 650). In *B* all blood vessels are patent, and there is no inflammatory reaction (hematoxylin and eosin stain; × 125).

but they, too, were undergoing degeneration, with the characteristic beading, swelling to much greater sizes than normal and, finally, fragmentation (fig. 2 *A*). Both the fragmented myelin and the axis-cylinders were phagocytosed before they had completely disintegrated (figs. 2 *B* and 3 *A*). There was no inflammation or increase in the connective tissue elements, and the blood vessels were normal (fig. 3 *B*). Most of the cells of the anterior horn were well preserved and normal, but a few were undergoing chromatolysis, and several were almost degenerated. Some of the glia cells in the regions containing normal myelin were swollen, occasionally contained two nuclei and had numerous short processes.

Longitudinal sections through the middle thoracic segments of the spinal cord disclosed similar but less pronounced changes. The axis-cylinders were undergoing ascending degeneration; they were irregular in course and outline and were swollen and beaded; many were fragmented. In this portion of the spinal cord the astrocytes were hypertrophic. In the anterior columns there was a small region of ascending degeneration. The majority of the ganglion cells of the anterior horns were normal, but a few were chromatolytic. In spite of the extensive regions of necrosis and the degeneration secondary to this profound transverse lesion, there was marked absence of corpora amylacea throughout the entire spinal cord.

Case 2.—A married woman, aged 28, had been subject to recurrent tonsillitis. Ten days prior to examination she noted numbness and tingling of her feet. This was followed within a day or two by a sensation of coldness and numbness which extended up the legs and which was accompanied by progressive weakness, so that within five days after the onset motor and sensory paralysis was present up to the waist. She had to be catheterized and given enemas because of obstipation. The numbness and weakness progressed, and at the time of examination, on Feb. 16, 1928, it had advanced to the shoulders. The left arm was weak; the right arm, less so. There was a sensation of constriction over the upper part of the abdomen.

Examination.—On February 16, the patient had a temperature of 101 F., and leukocytes numbered 8,900 in each cubic millimeter of blood. There were flaccid paralysis and complete anesthesia up to the level of the seventh thoracic segment. All the deep reflexes of the legs were absent. The abdominal reflexes were absent, and there was only a suggestion of a plantar extensor response on the right side. The deep reflexes of the arms were diminished. There were slight pallor of the left optic disk and what appeared to be central scotoma on a rough test. The Wassermann (Kolmer) test of the spinal fluid on February 18 gave negative results; the reaction to the globulin test was positive; there were 11 small lymphocytes in each cubic millimeter, and the colloidal gold curve was negative. There was evidence of partial block of the subarachnoid space. The level to which sensation was disturbed gradually ascended to about the eighth cervical segment. The exact level could not be determined, because after February 26 the patient cooperated poorly, owing to mental cloudiness. Examination of the spinal fluid a second time, on March 1, disclosed only 2 cells in each cubic millimeter. In the following two days the temperature gradually reached 105 F. The patient died on March 3, the entire length of the illness being three and a half weeks.

Necropsy.—There was a decubitus on the right buttock. There were no gross lesions in the peritoneal, pleural or pericardial cavities and no gross or microscopic lesion in the organs of the peritoneal or pleural cavities. There was a fish-mouth type of stenosis of the mitral valve, caused by old healed lesions of rheumatic endocarditis, but no recent exacerbation. There was a minimal degree of arteriosclerosis of the aorta; the ostia of all the intercostal vessels were patent, and there was no sclerosis of these smaller vessels. The cerebrum, midbrain, pons, cerebellum and medulla oblongata were normal on gross and microscopic examination. In the lower portion of the medulla oblongata there was obvious dilatation of the central canal. This dilatation extended throughout the entire length of the spinal cord, but to a lesser degree below the level of the cervical segments. The blood vessels of the spinal cord and meninges were normal. The entire spinal cord, from the level of the fifth cervical to the twelfth thoracic regions was softened, and it was impossible to distinguish the normal markings,

for the substance of the spinal cord was white and pultaceous and in parts almost fluid. Above and below these levels the tissue was firmer, and it was possible to distinguish the gray matter from the white. There was no evidence of hemorrhage in any part of the spinal cord.

Histologic examination of the lumbar segments of the spinal cord revealed normal structures, except slight early degeneration in the pyramidal tracts, which was demonstrated by the Marchi stain. At the level of the eleventh and twelfth thoracic segments the spinal cord was similar to that in the lumbar segments, except in the base of the posterior columns, where there was a small round region of degeneration of the myelin sheaths and axis-cylinders. This region of degeneration had been completely replaced by numerous scavenger cells which contained lipoid, particles of undegenerated myelin and fragments of axis-cylinders. There was no inflammatory reaction. In the middle of the thoracic portion of the spinal cord the meninges, nerve roots and blood vessels were normal. The myelin sheaths at the periphery of the spinal cord were normal, but the entire center was necrotic or degenerated (fig. 4 *A*). The degenerated area was irregular in outline and was more marked on the right side than the left, but all the columns were involved. The gray matter also was destroyed but was better preserved than the white, especially on the left side, where the ganglion cells of the anterior horn and of Clarke's column were preserved, although some gave evidence of chromatolysis. The surrounding white matter had degenerated and had been almost wholly replaced by scavenger cells containing free lipoid, undegenerated particles of myelin and fragments of myelin sheaths. Practically all the necrotic tissue had been phagocytosed, and there was no inflammation. There was no increase of connective tissue, although all the mesodermal elements had been preserved intact. The blood vessels were dilated, but the walls were normal, and there was no hemorrhage. There was no proliferation of the astrocytes in the preserved columns of myelin. The central canal was dilated, constituting a mild degree of hydromyelia, and the canal contained only a few small masses of débris. At the level of the third, fourth and fifth thoracic segments of the spinal cord there was complete destruction of almost all the myelin sheaths and axis-cylinders (fig. 4 *B*), and the center had been replaced by scavenger cells. Many of these cells contained granules of undegenerated myelin and pieces of fragmented axis-cylinders, as well as lipoid substance. The mesodermal elements had been preserved intact and were not increased. The blood vessels were slightly dilated but were otherwise normal. The degeneration of the gray matter was almost as profound as that of the white matter; several ganglion cells were preserved in the left anterior horn, but even these were undergoing chromatolysis. The astrocytes had suffered a fate similar to that of the other ectodermal structures; almost all had disappeared, except in the region of the anterior horns, where there were several hypertrophic astrocytes with large cell bodies and occasionally two nuclei. Sometimes mitotic figures were seen in proliferating and dividing scavenger cells, but this phenomenon was infrequent. The central canal was patent and slightly distended, but not to the degree observed at lower levels, and it contained no débris. The ependymal cells were normal.

The necrosis and degeneration had extended up to the lower end of the cervical enlargement, and the histologic changes were identical with those seen at lower levels, except that the ganglion cells of the anterior horns were better preserved. Even in the midst of the necrotic and degenerated anterior horns some ganglion cells persisted, but in most of these early signs of degeneration were apparent. At the middle of the cervical enlargement the anterior half of the spinal cord was normal. The posterior half had completely degenerated and was replaced

by scavenger cells. The other changes were identical with those noted in the upper thoracic and lower cervical segments. At the upper end of the cervical enlargement the area of necrosis was limited to a small zone in the base of the posterior columns. There was early ascending degeneration in the remaining

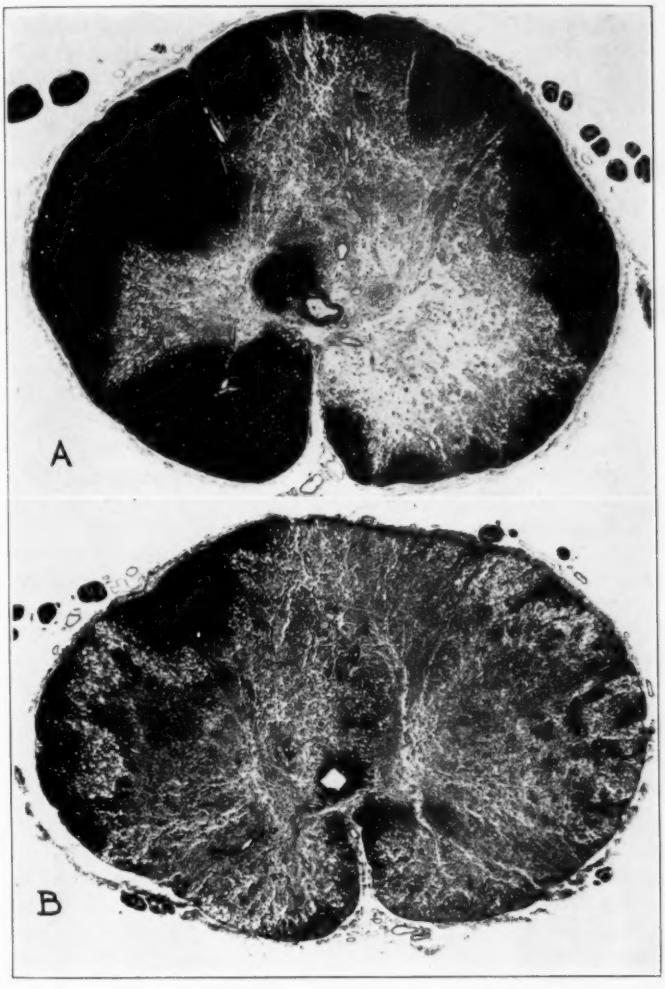

Fig. 4.—*A*, cross-section at the level of the eleventh and twelfth thoracic segments, showing necrosis of the greater portion of the center of the spinal cord. There is no inflammation; the blood vessels are normal, and there is no meningitis (Weigert myelin sheath stain; × 9½). *B*, cross-section at the level of the third, fourth and fifth thoracic segments, showing necrosis of practically the entire center of the spinal cord. Thrombosed blood vessels are absent. The central canal is dilated but contains no débris (Weigert myelin sheath stain; × 9).

portions of the posterior columns and the other ascending tracts. The other portions of these segments were normal. Most of the ganglion cells in the

anterior horns were normal. Above this level the spinal cord was normal, except for ascending degeneration.

Longitudinal sections of the cord confirmed the observations made on the cross-sections. The myelin sheaths and axis-cylinders were degenerated and fragmented, and the small portions had been phagocytosed by the scavenger cells before disintegration took place. The only reaction to the necrosis was phagocytosis of the débris. The gray matter, especially the ganglion cells of the anterior horns, was better preserved or else resisted the degeneration much better than the white matter. By comparing the myelin sheath stains and the stains for axis-cylinders it was seen that the axis-cylinders were better and more uniformly preserved than the myelin sheaths and that in many areas from which the myelin had completely disappeared there were many well preserved axis-cylinders, most of which did not show any sign of degeneration. The dorsal root ganglions from various levels were examined and were found to be normal.

Case 3.—A girl, aged 17, at the age of 5 had sustained a severe burn over the trunk and arms. A small area over the back had failed to heal. Six months before her visit to the clinic an unsuccessful attempt had been made to graft skin to this open area. After biopsy, on July 3, 1931, squamous cell carcinoma, graded 4, was reported. The patient was given a course of radium treatment over the back from July 7 to 10. An abscess developed in the left breast, which was drained on July 22. On July 24, the patient noted a drawing pain in the right side of the thorax, which radiated down the right arm. The next day there was a numb feeling from the right hip to the knee. The same day she observed numbness of the toes of both feet; this rapidly spread upward. On July 25, she was unable to move her legs, and examination, on July 27, disclosed motor and sensory paralysis up to the fourth thoracic segment, with paralysis of the bowel and bladder. Unfortunately, a notation as to the state of the reflexes was not made. The ocular fundi were normal. The temperature was 101 F., and leukocytes numbered 6,600 in each cubic millimeter of blood. The Wassermann (Kolmer) test of the spinal fluid gave negative results; the value for total protein was 160 mg. in each 100 cc.; there were 3 small lymphocytes, 3 large lymphocytes and 2 polymorphonuclear cells in each cubic millimeter; the colloidal gold curve was 4141333332; the pressure and color of the spinal fluid were normal. The neck was slightly rigid. The patient rapidly grew weaker, and on July 31 pneumonia developed. She died on August 6, after an illness of two weeks.

Necropsy.—The scars on the back and the carcinoma were noted. There was a decubitus over the sacrum, and the scars of the healed abscess were on the left breast. No gross or microscopic lesion was found in any of the organs of the abdominal or pericardial cavities. There was slight edema of the lungs, with beginning bronchopneumonia. In the lower portion of the upper lobe of the left lung was a small, firm nodule, 5 mm. in diameter, which on microscopic examination was seen to be an abscess. The kidneys were normal, but there was an acute inflammation of the bladder, with several small, superficial ulcers covered with exudate. There was no carcinomatous metastasis to any of the organs or lymph nodes of the body. The arteriosclerosis of the aorta and larger vessels was minimal, and there was no occlusion of the ostia of any of the intercostal or other arteries. Permission had been obtained to examine only the lumbar and lower thoracic portions of the spinal cord. There were no masses of carcinoma adherent to the dura mater; the arachnoid was also free from metastasis. The surface of the spinal cord was irregular and nodular. The nodules were pearly white and were most numerous over the posterior surface,

Fig. 5.—Nodular appearance of the spinal cord due to multiple herniations of the necrotic substance of the cord through ruptures in the pia mater.

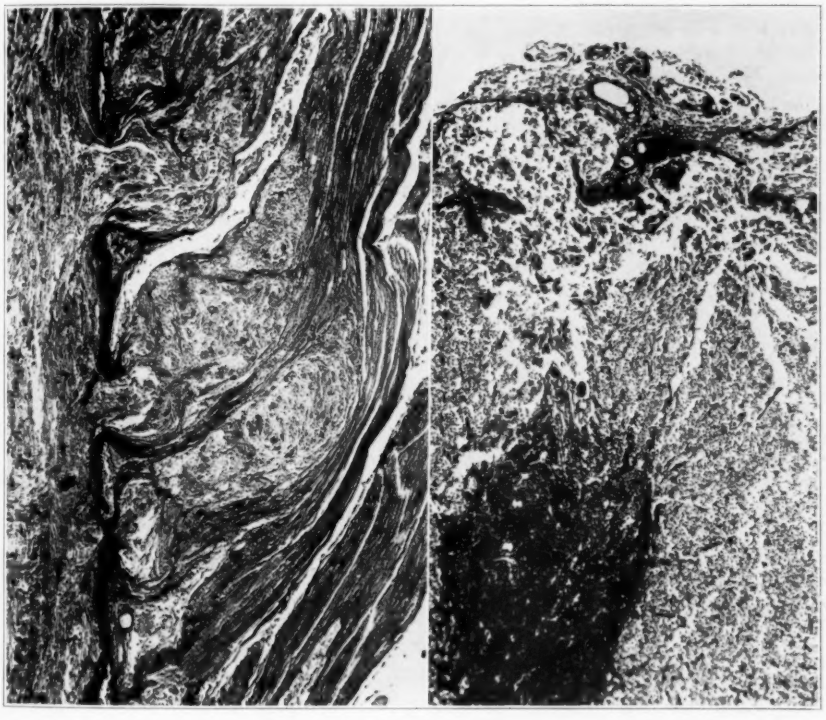

Fig. 6.—Photomicrographs showing extension of spinal cord débris through ruptures in the pia mater into the posterior nerve roots. There is no reaction on the part of the nerve roots (azo-carmine stain; × 40).

especially near the site of entrance of the posterior nerve roots, but they were not limited to these points of the spinal cord (fig. 5). The roots themselves were free. The nodules were soft and widespread. The spinal cord was diffusely white and soft, and the normal markings could not be seen, but there was no hemorrhage. The softening of the cord and the irregularities of outline extended into the conus medullaris and even down to the lower end of the filum terminale, which had a nodular, bulbous appearance. These nodules were considered to be metastatic from the carcinoma of the back.

On histologic examination no carcinoma cells were found in the spinal canal. The nodules on the surface of the spinal cord were herniations of the substance of the cord. The leptomeninges were thickened and adherent to each other, and there was an increase of connective tissue, which in places had undergone hyaline change. There was no inflammation. The blood vessels were normal and patent and were full of normal erythrocytes. There was complete necrosis of the spinal cord, without any reaction. The normal structure of the cord had disappeared; the myelin sheaths had disintegrated and fused so that their characteristic honeycomb appearance was lost; yet the white matter of the spinal cord stained diffusely blue with Weigert's myelin sheath stain.

The axis-cylinders were fragmented into very small pieces but gave no evidence of swelling, beading or other signs of disintegration. The gray matter was also necrotic, although it was possible to distinguish the ganglion cells, which retained their affinity for silver and thionine. The Nissl granules had disappeared, and the nuclei were eccentric. The glia cells had lost their affinity for all stains; only the nuclei were visible, but they were pyknotic, and the cell bodies could not be demonstrated. There were no polymorphonuclear leukocytes or lymphocytes, and there was no vital reaction of any kind; even scavenger cells were absent. The nerve roots entering and emerging from the spinal cord were normal. The only abnormality was the presence of extravasated necrotic substance of the cord, which had herniated through small ruptures of the pia mater at the entrance of the posterior nerve roots (fig. 6). The contents of the hernias stained in a manner similar to the necrotic spinal cord. There was no reaction where the necrotic substance of the cord came in contact with the normal nerve roots. The hernias were most numerous at the entrance of the posterior nerve roots, but there were many at the exit of the anterior nerve roots, and some were scattered diffusely in other parts of the spinal cord.

COMMENT

There was close similarity in the histologic observations in all three cases. In case 1 the walls of the smaller vessels were thickened, and their lumens were narrowed, as is seen in cases of severe and rapidly fatal hypertension. No history of high blood pressure was obtained, nor was high blood pressure present during physical examination. Vascular changes were not widespread through the body, as is the case in hypertension, but were limited to the lower portion of the spinal cord and its meninges. The necrotic changes in the substance of the spinal cord continued to higher levels. This suggested that the thickening of the meninges or the narrowing of the lumens of the small arteries and arterioles was not an etiologic factor, but such thickening of the meninges is by no means uncommonly observed by pathologists and neurosurgeons.

In cases 2 and 3 the blood vessels were normal. There were no changes in the larger vessels in any of the cases. In this respect these cases are different from those described by Foix and Alajouanine,[5] in which the larger vessels had irregularly thickened and laminated walls, giving them the appearance of cross-sections of an onion. Our patients were young and gave no evidence of generalized arteriosclerosis, except of a very mild degree, and the ostia of the intercostal arteries were normal.

Infarcts in all organs of the body produce necrosis, which in turn leads to the accumulation of large numbers of polymorphonuclear leukocytes and, later, of lymphocytes. Occasionally, infarcts with necrosis occur in the brain, but without any visible reaction; even scavenger cells are absent in the early stages. However, it could not be demonstrated in any of our cases that necrosis was the result of vascular occlusion, and there was no evidence of recent or old blood. Therefore, the changes observed were not the result of rupture of any blood vessels. The possibility that the changes observed in the substance of the spinal cord might be the result of poisoning by some heavy metal, such as lead or arsenic, was entertained. Chemical analysis showed that lead or arsenic was not present in the substance of the spinal cord in case 1 and case 2 or in the brain in case 2. It is remarkable that the ganglion cells should be preserved better than the myelin sheaths or axis-cylinders, because these structures are usually considered more delicate and respond more readily to destructive agents than the other components of the spinal cord. Further, the axis-cylinders survived the destruction of the myelin sheaths, which was especially remarkable in case 2; but even the axis-cylinders finally succumbed.

There are several diseases of the central nervous system which primarily affect the myelin sheaths. Of these, multiple sclerosis is the most common; but it is essentially a chronic disease and differs from that exemplified in the three cases reported, both in clinical course and histologic manifestations. Encephalitis periaxialis diffusa affects the brain, usually beginning in the occipital lobes and extending forward; the myelin sheaths are destroyed, and secondarily the axis-cylinders undergo degeneration, but the cortex and the nerve cells of the basal ganglions are not involved in the degenerative process. All the vessels are normal. The disease progresses rapidly and leads to a fatal termination within a few months. Many points of similarity exist between the condition in cases 1 and 2 and the disease referred to as encephalitis periaxialis diffusa. In these cases the myelin appeared to be primarily destroyed, and the axis-cylinders underwent degeneration secondarily. If the lesion was sufficiently extensive the ganglion cells became

5. Foix, C., and Alajouanine, T.: La myélite nécrotique subaiguë, Rev. neurol. **2**:1 (July) 1926.

disintegrated, but they persisted longer than either of the other two elements. There was also no evidence of inflammation, but there were numerous scavenger cells. The degeneration also progressed cranially, although the course was much shorter than in Schilder's disease. The astrocytes in the middle of the necrotic tissue degenerated and disappeared, but at the edge, especially in the lesions of longer duration, there was slight evidence of glial activity. The histologic differences could easily be accounted for on the basis of rapidity of progress and the short time available for a glial reaction to occur.

Herniation of the substance of the spinal cord through ruptures in the pia mater are rare, although they have been recorded by several observers. They seldom occur under normal conditions but appear when the spinal cord has been diseased and is necrotic. In case 1, in which we first noted them, they were not visible to the naked eye and were found only on microscopic examination. In case 3 the hernias were much larger, more numerous and more extensive. The herniated débris was composed mostly of scavenger cells containing free fat, phagocytosed and undegenerated masses of myelin and fragments of axis-cylinders, as well as unphagocytosed masses of the same material. The detritus had penetrated only short distances into the nerve roots, which appeared normal and healthy and did not seem to resent the presence of the material, which is normally foreign to this situation. There was complete absence of reaction on the part of the nerves and their mesodermal elements.

The association of necrosis of the spinal cord and malignancy has been noted, and we have found several recorded cases; however, the incidence is so small that the possibility of coincidence cannot be seriously considered. In our third case this association was present; it is the only case of this kind in the records of the Mayo Clinic. Metastasis, or extension to the subarachnoid space, causing so-called compression myelitis, has been frequently seen, but in this condition the changes in the spinal cord are not those of necrosis. The effect of metastasis to the brain on the contiguous brain tissue is well known, but even when the malignant process is in contact with the brain tissue it does not produce extensive necrosis, unless a blood vessel is obstructed. In case 3 the patient suffered from a highly malignant carcinoma of the skin, which had been treated lightly with radium. At the time of the patient's death this malignant tumor had not metastasized, and the spinal canal was free from carcinoma cells. Radium, even in heavy doses, does not affect the spinal cord by producing necrosis. We believe that both the carcinoma and the necrosis caused by radium were incidental to the acute degeneration which occurred in the spinal cord. The onset of the lesion of the spinal cord was abrupt; progress was rapid, and

degeneration was extensive. It is impossible to conceive a necrotic condition in any organ of the body, except the central nervous system, in which there is no reaction to the necrosis. In case 1 the necrosis had existed thirty-four days, but in the lumbar region, where the lesion was oldest and most extensive, there was only a slight invasion by scavenger cells. In case 3 there was complete absence of reaction, even after thirteen days, although, had the patient lived longer, reaction and scavenger cells would, undoubtedly, have appeared.

Case 3 differed from cases 1 and 2 in the severity of the necrosis and in the degree of cellular reaction. The myelin sheaths were disintegrating, but no evidences of degeneration, such as swelling, loss of ability to stain or breaking down into component parts, were present, and the normal structure and outline of the myelin sheaths were not visible. The axis-cylinders were not swollen, beaded or vacuolated but were broken into very small fragments which retained their affinity for silver. The gray matter was also necrotic, and although the ganglion cells were easily distinguished they stained diffusely and not specifically with thionine. These changes were such as might be expected as the result not only of sudden and complete interruption of the blood supply but also of interruption of all circulation of fluid in the substance of the spinal cord. In spite of this, all the blood vessels in and around the spinal cord were normal. There was no proliferation of the endothelium lining the smaller vessels, such as would have been present had the blood flow been interrupted between the aorta and the vessels of the spinal cord.

There was no apparent common etiologic factor. The clinical course of the disease was essentially the same in the three cases, whereas the pathologic picture was predominantly that of necrosis without any inflammatory reaction.

In the older literature cases of spinal necrosis were described under the general heading of myelitis, and it was not until the rather bitter controversy between Leyden,[6] of the old school, and the young and progressive Oppenheim [1] that any marked progress developed. Leyden held to the old classification of myelitis, while Oppenheim had put his approval on a revision of the classification of diseases of the spinal cord. The latter considered true myelitis a rare disease, and he stated that in eight years (from 1883 to 1890) he had seen only two cases of myelitis at postmortem examination. Marie [7] even went so far as to say that primary myelitis did not exist.

6. Leyden, E.: Beiträge zur acuten und chronischen Myelitis, Ztschr. f. klin. Med. **1**:1, 1879; Ueber akute Myelitis, Deutsche. med. Wchnschr. **18**:621 and 648, 1892.

7. Marie, P., quoted by Rhein, J. H. W.: A Pathological Study of Acute Myelitis, Univ. Pennsylvania M. Bull. **17**:373 (Jan.) 1905.

In 1922 Bassoe called attention to three cases of myelomalacia, which presented similar clinical and pathologic pictures—one, his own,[8] the others, reported by Feindel[9] and Schmitt.[3] Bassoe's case was that of a woman, aged 45, who died about five and a half months after the onset of the illness, which had followed sore throat. On section of the cord the following striking features were observed: The entire thoracic cord was a creamy mass and contained cavities; there was less injury in other portions; inflammatory reaction was absent; all ectodermal elements were markedly degenerated; glia had been found; gitter cells were present, and regressive changes were absent. Hassin[8] stated that the "yellow softening" was the same as in encephalomalacia and that since this was not an inflammatory condition the myelomalacia was caused not by myelitis but by degeneration. In Bassoe's patient, as in one of ours, there was pallor of one optic disk. Schmitt's case was similar. There was extensive softening from the fourth thoracic to the first lumbar segment, with no inflammatory reaction or exudate. Feindel's case is of interest in that it occurred in a man, aged 23, who had a sarcoma of the leg and who was treated by the injection of arsenical preparations. Feindel suggested that the cause of the necrosis was a toxic infectious process due to the lowered resistance of the patient and to the use of arsphenamine.

Since our cases appeared to be similar to those described, we carefully studied the reported cases and were able to assemble six, including the three mentioned by Bassoe, which, we believe, belong in this category. D'Antona's[10] case of spinal necrosis and adenocarcinoma of the lung, with metastasis to the ribs and liver, was the next published; it resembled rather closely that of Feindel. D'Antona considered the condition to be carcinotoxic myelodegeneration, a term first used in this connection by Nonne.[11a] In this patient some slight changes were found in the blood vessels, and there were a few hemorrhages. D'Antona thought that vascular changes may have played a part in the causation of necrosis, although the evidence was slight. It was also noted in this case that there were small hernias of the substance of the cord, such

8. Bassoe, P.: Nervous and Mental Diseases, Practical Medicine Series, Chicago, Year Book Publishers, 1920, p. 125; Bassoe, P., and Hassin, G. B.: Myelitis and Myelomalacia, Arch. Neurol. & Psychiat. **6**:32 (July) 1921.

9. Feindel, R.: Ueber akute aufsteigende Rückenmarksnekrose, Ztschr. f. d. ges. Neurol. u. Psychiat. **68**:147 (July) 1921.

10. d'Antona, S.: Sulla necrosi spinale acuta nel corso dei tumori maligni, con un contributo alla conoscenza delle "ernie spinali malaciche," Neurologica **3**:65 (April) 1926.

11. Nonne, M.: (*a*) Ueber acute Querlähmungen bei maligner Neubildung der Wirbelsäule, Berl. klin. Wchnschr. **2**:728, 1903; (*b*) Myelodegeneratio transversa carcino-toxaemia, Med. Klin. **2**:943, 1919.

as have been described by Nauwerck.[12] A similar finding was made for two of our patients. Low [13] searched for some evidence of thrombosis in his case but found none. He recovered a gram-positive streptococcus from the cord but doubted if this was a dependable finding. Stone [14] described a case under the proper heading of myelomalacia but found no evidence of thrombosis, even though he thought that thrombosis should be the cause. In the discussion of this case before the Chicago Neurological Society, Hassin and Patrick emphasized the rarity of primary myelitis and stated that myelomalacia was the more frequent finding. It is noteworthy that Schmitt, Low and Stone all used the term myelomalacia rather than myelitis.

The table gives a brief summary of these cases and of ours. Five of the patients had had some preceding infection; three had an associated malignant condition which did not affect the central nervous system directly but which may possibly have acted as a toxic agent. The duration of the illness varied between two weeks and six months. The spinal fluid usually contained an increased concentration of globulin, and the number of cells was moderate. Three patients had yellow spinal fluid, whereas in one case the spinal fluid was reported as normal. In one case the spinal fluid was not examined. All these cases were characterized pathologically by marked necrosis, especially of the white matter; there was little, if any, inflammatory reaction, and only moderate glial reaction. In our three patients the globulin in the spinal fluid was increased and the number of cells was moderate.

In addition to this group of cases, there is a large group which must also be reviewed. Some of these appear to belong in the category here identified, and since space will not permit extended consideration it must suffice to mention the relevant reports. The early cases of Oppenheim, Jolly and Nonne must be eliminated, because of incomplete data. In 1905, Rhein,[15] of the University of Pennsylvania, reviewed fifty-four cases of acute myelitis which came to necropsy and found that the majority were of the inflammatory type. His second case was that of a woman, aged 39, who died after an illness of thirty-two days, in whose spinal cord there was only moderate necrosis. This case must

12. Nauwerck, C.: Rückenmarkshernien, Centralbl. f. allg. Path. u. path. Anat. **34**:556 (June) 1924.

13. Low, A. A.: Acute Ascending Myelomalacia, with Clinical Picture of Landry's Paralysis; Clinicopathologic Report of Case, Arch. Neurol. & Psychiat. **21**:594 (March) 1929.

14. Stone, T. T.: Myelomalacia, Arch. Neurol. & Psychiat. **21**:718 (March) 1929.

15. Rhein, J. H. W.: A Pathological Study of Acute Myelitis, Univ. Pennsylvania M. Bull. **17**:373 (Jan.) 1905.

Summary of the Three Cases Reported in the Text and of Similar Cases Reported in the Literature

Case	Author and Date	Age, Years	Sex	Etiology	Duration, Weeks	Clinical Findings	Spinal Fluid	Postmortem Observations
1	Bassoe and Hassin, 1921.....	45	F	Sore throat (?)	22	Motor and sensory paralysis up to fourth rib; knee and achilles reflexes absent; no Babinski sign; pallor of right disk; temperature from 98 to 104 F.; leukocytes, 12,100	Wassermann reaction weakly positive (later negative); globulin reaction, 1+; cells, 26; colloidal gold curve 4333211100	Thoracic part of cord semifluid; demyelinization, no inflammatory reaction; infiltration by gitter cells; glia formation
2	Feindel, 1921.....	23	M	Sarcoma, arsphenamine (?)	3	Motor and sensory paralysis up to arms; onset of paralysis with fever	No examination of spinal fluid made	Lumbar and thoracic parts of cord swollen and reddish; demyelinization; gitter cells; fat-containing cells; no inflammation
3	Schmitt, 1921.....	17	M	Infection of tongue (?)	8	Motor and sensory paralysis up to waist; pains in arms; deep reflexes of legs absent; Babinski sign (?)	(1) Wassermann reaction negative; globulin reaction, 1+; cells, 14; (2) yellow fluid; cells, 1,052	Degeneration from fourth thoracic to first lumbar segments; other regions of degeneration; no inflammation
4	d'Antona, 1926.....	41	M	Carcinoma of lung (?)	8	Motor and sensory paralysis up to umbilicus; deep reflexes very weak; plantar reflexes (?)	Wassermann reaction negative; globulin reaction; 1+; protein, 60 mg.; many erythrocytes; many polymorphonuclear cells; few lymphocytes; yellow fluid	Many small nodules from fifth thoracic to third lumbar segments; cord gelatinous; hernia; marked necrosis but no inflammatory reaction
5	Low, 1929.....	30	F	Abortion (?)	9	Motor and sensory paralysis up to tenth thoracic segment; deep reflexes absent; temperature from 102 to 104 F.	Wassermann reaction. negative; globulin reaction, 1+; cells, 338	Softening of lower thoracic, lumbar and sacral parts of cord; very slight infiltration with lymphocytes; no thrombosis
6	Stone, 1929.....	26	F	Influenza, (?)	6	Motor and sensory paralysis up to upper limbs; deep reflexes of legs absent; no Babinski sign	Normal	Regions of softening from lumbar to cervical portions; gitter cells; no inflammatory reaction; no thrombosis
7	Moersch and Kernohan, 1933	37	M	Unknown	5	Complete ascending motor and sensory paralysis from fifth to seventh ribs; deep reflexes of legs absent; no Babinski sign; temperature from 99 to 104 F.; leukocytes, 17,400; decubitus and pyelitis	(1) Many erythrocytes; negative smear; (2) Kolmer reaction, negative; protein, 60 mg.; globulin reaction, 1+; 176 lymphocytes; 59 polymorphonuclear cells; slightly yellow fluid	Cord soft; marked demyelinization; very little inflammatory reaction; some destruction of axis-cylinders; moderate number of scavenger cells; no glia formation; hernia
8	Moersch and Kernohan, 1933	28	F	Recurring tonsillitis (?)	3½	Acute ascending motor and sensory paralysis up to shoulder girdles; deep reflexes of legs absent; deep reflexes of arms diminished; Babinski sign on right (?); slight pallor of left disk	(1) Kolmer reaction, negative; globulin reaction, 1+; lymphocytes, 11; partial block; (2) two cells; negative cultures	Cord softened; normal markings obliterated; no inflammatory reaction; marked necrosis of white matter and, to a less extent, of gray matter; degeneration of myelin and axis-cylinders; scavenger cells very numerous
9	Moersch and Kernohan, 1933	17	F	Carcinoma (?); abscess (?)	2	Acute paralysis up to fourth thoracic segment; temperature, 101 F.; leukocytes, 6,600; no notation made of reflexes; decubitus	(1) Kolmer reaction, negative; protein, 160 mg.; globulin reaction, +; 6 lymphocytes; (2) polymorphonuclear cells; colloidal gold curve, 4141333333222; negative cultures	Profound necrosis; no metastasis; demyelinization and fragmentation of axis-cylinders; no reaction of any type; hernia

be considered as at least a possible addition to the group. Buzzard,[16] in 1907, reported the case of a man, aged 44, who died after thirteen days of ascending paralysis. Postmortem examination disclosed destruction of myelin and axis-cylinders, but there was such an extensive inflammatory reaction that the case can scarcely be included. Globus,[17] in 1917, reported the case of a man who had died within forty-two hours of what the author termed acute ascending toxic myelitis. The cord was almost devoid of any inflammatory changes, and it is possible that the rapid death precludes any definite classification. In 1919, Nonne [11b] published in a report of a group of cases one that probably belongs with the cases of progressive necrosis of the cord. The patient was a man, aged 65, who had a carcinoma of the lung, with metastasis to various organs and to the bodies of the eighth to the twelfth thoracic vertebrae. Sections of the cord disclosed definite necrosis. Wohlwill and Jakob examined the tissue and substantiated Nonne's findings. If this case belongs to our present group, it is the first one reported in the literature that can be included.

There is, in addition, a group of cases reported by various authors, such as von Economo,[18] Spiegel,[19] Harris,[20] Pussep [21] and others, in all of which there was myelitis associated with grip or encephalitis. In all these cases, however, there was so much evidence of inflammation that they cannot be included in this group. Another group of cases, described later, namely, those in which the lesion was of vascular origin, reported by Spiller,[22] Guy, Schaller [23] and Winkelman and Eckel,[24] must be mentioned, but these cannot be confused with cases of progressive necrosis, since in these cases the vascular lesions were at least considered to be the cause of the softening. Winkelman's second case

16. Buzzard, E. F.: On Certain Acute Infective or Toxic Conditions of the Nervous System, Brain **30**:1 (June) 1907.

17. Globus, J. R.: Acute Ascending Toxic (or Degenerative) Myelitis, J. A. M. A. **69**:816 (Sept. 8) 1917.

18. von Economo, C.: Grippe-Encephalitis und Encephalitis lethargica, Wien. klin. Wchnschr. **32**:393 (March) 1919.

19. Spiegel, E.: Myelitis nach Grippe, Wien. klin. Wchnschr. **32**:258, 1919.

20. Harris, A. F.: Report of a Case of Epidemic Encephalitis with Cord Changes Suggestive of the Possibility of an Early Syringomyelia, Am. J. Psychiat. **1**:679 (April) 1922.

21. Pussep, L.: Akute aufsteigende Myelitis als Komplikation der Influenza, Ztschr. f. d. ges. Neurol. u. Psychiat. **87**:377, 1923.

22. Spiller, W. G.: Rapidly Developing Paraplegia Associated with Carcinoma, Arch. Neurol. & Psychiat. **13**:471 (April) 1925.

23. Schaller, W. F.; Roberts, A. M., and Stadtherr, E. F.: Acute Myelitis (Myelomalacia); Syndrome of Occluson of Anterior Spinal Artery at Fifth Cervical Cord Segment, J. A. M. A. **99**:1572 (Nov. 5) 1932.

24. Winkelman, N. W., and Eckel, J. L.: Focal Lesions of the Spinal Cord Due to Vascular Disease, J. A. M. A. **99**:1919 (Dec. 3) 1932.

may belong to the group that we are considering, for even though he thought that it was caused by a vascular lesion he was unable to find any such lesion.

In 1926, Foix and Alajouanine [5] reported two cases under the heading of subacute necrotic myelitis. The cases were essentially identical. One patient lived eleven months; the other, two and three-fourths years. The authors emphasized certain features in the cases, such as amyotrophic paraplegia, increased protein in the spinal fluid, few cells, subacute evolution, early dissociation of sensory findings, extensive necrosis (mainly in the gray matter) and, finally, marked changes in blood vessels, especially of the endomesial type. It would appear that these two cases are closely related to those of our series, and it is possible that the authors laid too much stress on the vascular changes, which may have been of secondary rather than of primary importance. They thought, however that they were dealing with something different from multiple sclerosis or myelomalacia. Several similar cases were reported by Van Gehuchten,[25] Lhermitte [26] and Van Bogaert. In reviewing these cases, it is a question whether they should be isolated in a separate group or included in the group in which we are interested.

Reports of four cases were recently published by Davison and Keschner.[27] These authors expressed the belief that their cases represented a toxic myelopathy in which the clinical picture is fairly uniform but which cannot be distinguished clinically from infectious myelitis. The histopathologic picture consisted of marked destruction of myelin sheaths and axis-cylinders, poor glial reaction and only slight changes in the anterior horn cells and blood vessels. Their case 1 was so similar to our cases that we believe that it should undoubtedly be considered under the same heading. The other three cases seem less certain, for the necrosis was at the periphery and not in the center of the spinal cord and was also less profound. In their discussion of myelitis the authors stressed the rarity of infectious myelitis and attempted to classify the nonsystemic disease of the cord under two general headings, namely, myelitis and myelopathy.

It is interesting that among the cases which we have reviewed, including one of ours, the condition in three was apparently secondary to malignancy. Just what this relationship may be we do not know, but it must be emphasized that in these cases there was no destruction

25. Van Gehuchten, P.: Un cas de myélite nécrotique aiguë, Rev. neurol. **1:** 505 (April) 1927.

26. Lhermitte, J.; Fribourg-Blanc, A., and Kyriaco, N.: La gliose angéiohypertrophique de la moelle épinière (Myélite-nécrotique de Foix-Alajouanine), Rev. neurol. **2:**37 (July) 1931.

27. Davison, C., and Keschner, M.: Myelitic and Myelopathic Lesions; Clinicopathologic Study; Myelitis, Arch. Neurol. & Psychiat. **29:**332 (Feb.); 600 (March) 1933.

of the spinal cord by metastasis and that in our case there was no evidence of any metastatic lesion elsewhere in the body. In this connection Nonne and others have written of carcinotoxic degeneration, which, however, does not help to clear up the problem. It is well to recall that carcinoma growing in the substance of the central nervous system does not produce any reaction such as was seen in these cases.

The possibility that this type of necrosis of the spinal cord is secondary to intoxication by lead has been considered. In none of our cases and, so far as we could gather, in none of those recorded in the literature was there any exposure to lead. On examination of the spinal cords in two of our patients and of the brain in one, search for evidence of lead gave negative results.

It is impossible to review all the cases and mention all the considerations which enter into this still unsolved problem. One must refer to Beck's [28] case to emphasize the point already mentioned, namely, the similarity between this condition and encephalitis periaxialis diffusa or acute multiple sclerosis. To consider the condition to be Schilder's disease of the spinal cord is not helpful. Spiegel's [19] case, reported in 1919, should also be considered in this discussion.

CONCLUSIONS

Our study shows that a clinical diagnosis of progressive central necrosis is difficult. It has been frequently noted in diseases of the cord that even when the clinical pictures are similar the pathologic findings may be surprisingly different, depending on whether the cause is infectious, toxic, necrobiotic, vascular or unknown. The converse of this statement also holds true. It appears that if a patient can withstand the tremendous insult of the acute attack and does not succumb to a secondary infection, life can be sustained for many months and even for several years. Thus far we have gained no clear conception as to the etiologic factors present in our group of cases. There was a markedly febrile course in all, but no organisms were found in the spinal fluid. Much could be said regarding the possibility of the presence of a virus, but although the existence of such an agent is probable, this was not susceptible of proof at our hands. To assume the existence of a toxic agent appears to be inadvisable, at least without more data, for it may be that, in spite of our findings, some vascular or even infectious agent may be playing a part. Hassin stated that the conditions may be of infectious, degenerative or necrobiotic origin, but he, too, seemed uncertain in this regard. We present these observations, hoping that they may lead to a clearer understanding of diseases of the spinal cord and not with the idea of causing added confusion.

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28. Beck, G. M.: A case of Diffuse Myelitis Associated with Optic Neuritis, Brain **50**:687, 1927.

DISCUSSION

DR. PETER BASSOE, Chicago: I am impressed by the history of some sort of infection in most of these cases, and, in spite of the absence of inflammatory changes, it seems to me that there is strong reason to believe that we are dealing with focal necrosis due to bacterial products. In this report, excellent from both the clinical and the neuropathologic point of view, I miss reference to a bacteriologic examination. I wish that Dr. Rosenow or some one like him had been called in to make a thorough bacteriologic examination not only of the central nervous system but also of the rest of the body. Some bacteria have a marked tendency to produce necrosis of tissue; for instance, some organisms that produce conditions usually classified under influenza.

DR. GEORGE B. HASSIN, Chicago: The interesting cases presented by Dr. Moersch and Dr. Kernohan are pathologically what is generally termed myelomalacia, or softening of the spinal cord. This is usually caused by a vascular disorder, such as thrombosis or embolism, but it may also be caused by an infectious toxic agent. In the latter case not only the parenchyma but also the glia may be affected, as was so well brought out in Alzheimer's laboratory by Rosenthal and especially by Lotmar. By injecting toxins of dysentery, Lotmar produced in animals two types of changes in the brain and cord, depending on the amount of toxin injected, the age of the animal and other factors. He designated these changes, probably wrongly, as toxic encephalitis and toxic myelitis. In one type of changes only the parenchyma of the nerve became affected, while the glia exhibited marked reactive phenomena. Lotmar termed such glia "efficient." In other cases both the parenchyma and the glia succumbed to the action of the toxin; the glia showed no reaction and was, according to Lotmar, "deficient." It is remarkable that the difference in the glial reaction also affects the clinical picture. The course is more protracted in cases in which the glia is efficient, though the prognosis is bad in both types of softening. The type of softening of the cord in which both the parenchyma and the glia perish would probably be properly classified as necrosis.

DR. FREDERICK P. MOERSCH, Rochester, Minn.: In answer to Dr. Bassoe, Dr. Rosenow did see one of these patients, and I think that he found a streptococcic organism. In two of the cases the spinal fluid cultures were sterile.

So far as the etiology is concerned, that question remains unanswered. We examined two of these cords and one of the brains for lead; the results were negative. Whether we are dealing with a toxic or an inflammatory condition remains for further investigation to reveal.

In reply to Dr. Hassin, we debated for a long time as to what term to use in describing this condition. If one reviews the literature, one will find various terms employed. In 1926, Foix and Alajouanine reported cases under the heading of subacute necrotic myelitis, but they emphasized the tremendous change in blood vessels, which is seemingly absent in the cases which we reported. I do not know what term to use. This group of cases is probably the result of some toxin or virus and should be distinguished from cases that are the result of purely vascular or so-called degenerative changes.

HISTOLOGIC CHANGES IN THE BRAIN IN CASES OF FATAL INJURY TO THE HEAD

V. CHANGES IN THE NERVE FIBERS

CARL W. RAND, M.D.
AND
CYRIL B. COURVILLE, M.D.
LOS ANGELES

In this series of investigations on the histologic changes in brain tissues following injury, it has been our object to study separately the alterations in the various structures and elements. In previous investigations we have been concerned with the reaction of the choroid plexus and ependyma and the interstitial structures of the brain tissue proper. Working on the assumption that the epithelial cells of the choroid plexus and, to a lesser extent, those of the ependyma have a secretory function, we found that evidences of such activity were more abundant after injury than in the normal subject. The reaction of the interstitial elements was found to be concerned with the protection of the parenchyma from an increased amount of tissue fluid (oligodendroglia), with the removal of hopelessly damaged tissue (microglia) and, finally, with the process of repair (neuroglia). Interesting as these studies have been, they leave unanswered many important questions of practical value from the clinical standpoint as the modus operandi of symptom production.

It may be assumed from a mechanistic standpoint that the normal function of the brain is dependent on two factors: first, the initiation of impulses within the nerve cells and, second, their transmission over the complex, ramified nerve fiber network. On this premise it may be assumed that evidences of disturbed function may be due either to absence of initiation or to the initiation of subminimal impulses or of perverted and abnormal ones. Carrying the concept still further, symptoms may also be produced by a partial or complete interruption of normal or abnormal impulses, or perhaps by a redistribution of these impulses, so that new reaction patterns are produced. The problem of symptom production following head injury may be reduced to its simplest form if it can be determined how trauma interferes with the normal nervous mechanism. It must be admitted from the outset that

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our investigations have been concerned entirely with alterations in structure and that alterations in function may only be conjectured by making certain deductions from a study of injured nerve cells and fibers.

In the past, most considerations of neurologic symptoms produced by head injury have been largely clinical and predominantly theoretical, concerning themselves chiefly with the concept of concussion (commotio cerebri). This concept is concerned with a loss of consciousness due to a deleterious effect on the nerve cell itself. The influence of this general belief has apparently overshadowed the possibility of the interruption of nervous impulses by injury to nerve fibers and the rôle that such interruptions might play in the production particularly of late clinical symptoms.

In exploring the possibilities of symptom production consequent to changes in the nerve fibers, certain questions present themselves. What types of traumatic lesions are capable of provoking demonstrable changes in nerve fibers? In the absence of gross injury can nerve fibers be damaged without accompanying cellular injury? Is the nerve fiber more or less resistant to injury than the nerve cell? What changes take place in interrupted nerve fibers, and what are their significance? What, if any, are the attempts at regeneration of nerve fibers in the human central nervous system? To what degree may nerve fibers be injured and recover? What are the histologic characteristics of the successive stages of injury to nerve fibers? What is the ultimate fate of damaged or interrupted nerve fibers? What rôle does injury of nerve fibers play in the production of immediate or remote clinical manifestations? It is our purpose in this study to consider the various gross lesions capable of producing injury to nerve fibers, to investigate the histologic characteristics of such changes and to emphasize their possible connection with the clinical manifestations of head injury.

REVIEW OF THE LITERATURE

As in previous studies on changes in the interstitial elements consequent to injury, we find ourselves again largely dependent on the investigations of Cajal and his co-workers for a basis for the present investigation. For years these investigators concerned themselves with detailed changes in the nervous system following experimental injury.[1] As a matter of fact, their experimental work has been so fundamental

1. After a preliminary report in 1907 (Note sur la dégénérescence traumatique des fibres nerveuses du cervelet et du cerveau, Trab. d. lab. de invest. biol. Univ. de Madrid **5**:105, 1907), Cajal reported a series of studies on degenerative changes in the nerve cells and fibers of the brain following experimental injury. A résumé of this work has recently been translated into English (Degeneration and Regeneration of the Nervous System, New York, Oxford University Press, 1928, vol. 2), which makes the results of these studies more readily accessible.

and complete as to make further experimentation along this line almost unnecessary. While no doubt penetrating wounds of the brain would furnish more nearly a human counterpart of Cajal's experiments on animals, such material has not been available. Furthermore, traffic and industrial accidents resulting in brain injury at present create the greater proportion of our clinical problems.

As this study has proved to be an application of Cajal's methods to human brain injury, it seems advisable to analyze his observations of changes in the nerve fibers after experimental section. Attention will be drawn to (1) preservation necrosis, (2) degenerative phenomena of the peripheral stump and (3) traumatic degeneration of the central stump.

Preservation Necrosis.—Cajal found that the cerebral nerve fibers of young experimental animals were highly susceptible to the mechanical effects of trauma and that their instantaneous death was produced by comparatively minor injuries. Such injuries produced the phenomenon described by him as preservation necrosis.[2] This type of necrosis was characterized by the persistence of nerve fibers of essentially normal and uniform caliber, which were intensely impregnated with reduced silver. The findings which suggested pathologic change were the flexuous, spiroid or curved course, together with an absence of reactive change in the stump adjacent to the injury. This stump terminated in a point of corrosion, characterized by the formation of a tapering hook which became pale and ultimately disintegrated. According to Cajal, "in the phenomenon of preservation a great part is played by some antiautolytic principle which proceeds from the sanguineous exudate and is fixed in the protoplasm of the axon." He indicated that the first evidence of preservation appears within a few hours after injury and subsists, with variations, for from four to six days.

In studying degenerative changes in nerve fibers, Cajal followed the same order as in the study of peripheral nerve degeneration, i. e., investigation of the changes in the peripheral and central segments. He studied these changes at points distant from and near the cell of origin. He found that the intensity of degenerative change was directly proportional to the proximity of injury of the nerve fiber to the cell of origin and that the histologic characteristics of the change were constant in fibers of a given size.[3]

Interruption of Nerve Fibers in the White Matter.—Degenerative Phenomena of the Peripheral Stump: Regardless of the distance of the injury from the cell of origin, the peripheral segment of the nerve

2. Ramón y Cajal, S.: Fibras nerviosas conservadas y fibras nerviosas degeneradas, Trab. d. lab. de invest. biol. Univ. de Madrid **9**:181, 1911.

3. Ramón y Cajal, S.: Los fenómenos precoces de la degeneración traumatica de los cilindros-ejes del cerebro, Trab. d. lab. de invest. biol. Univ. de Madrid **9**: 39, 1911.

included two successive portions: a short necrotic segment and a segment of traumatic degeneration. When the nerve was sectioned in the white matter the necrotic segment of the peripheral stump, instantly disorganized by mechanical force, was found to be liquefied and absorbed within a few hours after injury. The remaining segment of traumatic

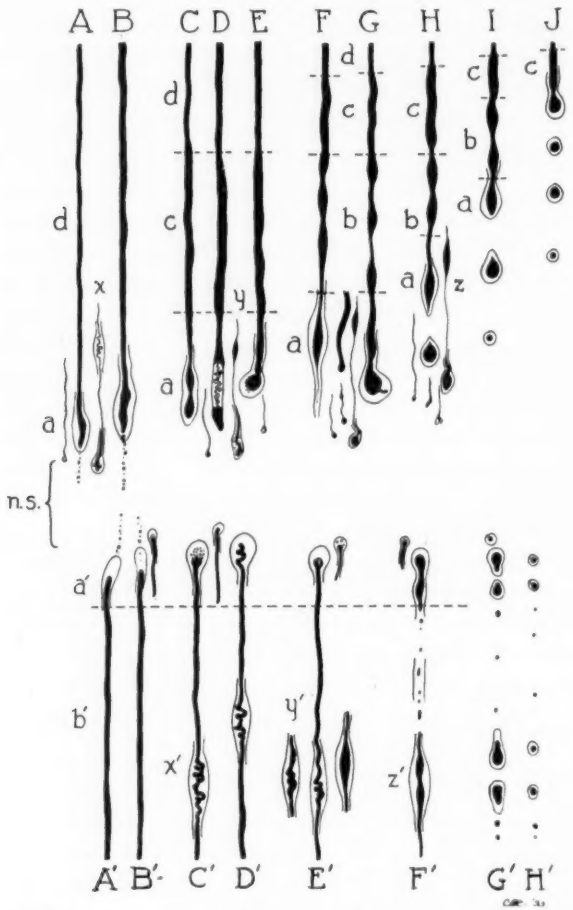

Fig. 1.—Changes in nerve fibers following experimental division deep in the white matter, according to Cajal. *A* to *J* represents changes in the proximal segment: *a*, a segment of the terminal ball; *b*, a varicose segment; *c*, a hypertrophied segment; *d*, a normal fiber; *n.s.*, a necrotic segment; *x*, *y* and *z*, the formation of fusiform swelling from local twists in smaller nerve fibers (the formation of end-bulbs and rings on the terminations of fine fibers is also indicated at the same intervals—*A* and *B*, one hour; *C*, *D* and *E*, six hours; *F* and *G*, twenty-four hours; *H*, *I* and *J*, following days). *A'* to *H'* represent changes in the distal segment: *a'*, an end-bulb; *b'*, a distal fiber; *x'*, *y'* and *z'*, the formation of single and then double fusiform swelling from local corkscrew twists in the nerve fiber (*A'* and *B'*, two hours; *C'* and *D'*, six hours; *E'*, eight hours; *F'*, two days; *G'* and *H'*, following days).

degeneration underwent a series of characteristic changes. From five to eight hours following injury, initial terminal retraction balls or rings were observed which had a characteristic structure. There was a peripheral hyaline ball in the center of which perfectly stained nerve fibrils formed a series of complicated nets and loops. About the same time, varicosities were observed along the fibers adjacent to the terminal ball. In these varicosities, convolutions of the axon were found to be present as late as from seven to eight hours following section of the nerve fiber. Somewhat more distal fusiform dilatations were observed, resulting from fusion of series of preexisting coils. In the course of two or three days the varicosities had begun to resolve themselves into free balls, which subsequently underwent digestion. During the same period granular degeneration of long stretches of axons were observed. The changes resulting from the section of nerve fibers deep in the white matter, as described by Cajal, are shown in figure 1.

If the nerve fibers had been sectioned nearer the cell of origin, i. e., in the lower levels of the cortex itself, the necrotic segment and the segment of traumatic degeneration were again distinguished. The necrotic segment was again rapidly absorbed. The changes in the segment of degeneration depended on the size of the fiber. Small autotomized balls were found in the region of the wound, attached to fine fibers. The large terminal balls were found to be in continuity with the larger axons and were divided into three parts: a sphere, ball or club; a thin appendix, and a hypertrophic segment (fig. 2). After between twenty-four and forty-eight hours the balls were characterized by a dark neurofibrillar network and a large peripheral zone of neuroplasm. The terminal appendix had its origin in one or two small neurofibrillar loops toward the apex of the club, evidently the remains of the axon between the ball and the wound, the neurobion of which had retracted to form the loops in the club. After from two to three days, the appendix had become shortened and retracted and the ball had become more hyaline and was surrounded by a digestion chamber. Some of the balls had become free, giving rise to bizarre, complicated, netlike structures in large spheres. The neurofibrillar loops and bundles in the balls became pale and granular and ultimately disappeared, so that the sphere was composed of a pale granular substance. These balls "represent agonistic neurofibrillar reactions, destined shortly to cease." Cajal intimated that they undergo progressive granular degeneration.

Traumatic Degeneration of the Central Stump: In his description of changes in the central stump, Cajal again considered the distance of the point of section from the cell of origin and the size of the nerve fiber concerned. When fine medullated or nonmedullated fibers were sectioned at a distance from the cell of origin, the short necrotic segment was quickly resorbed, while the segment of degeneration soon formed a

terminal or retraction ball. This retraction ball at the end of four hours consisted of a peripheral, colorless hyaline mass and a central glomerulus of neurofibrils, at first arranged in loops and spirals and later fusing into a compact central grume. At the end of three days these balls had resulted in the formation of double rings or loops, autotomized rings

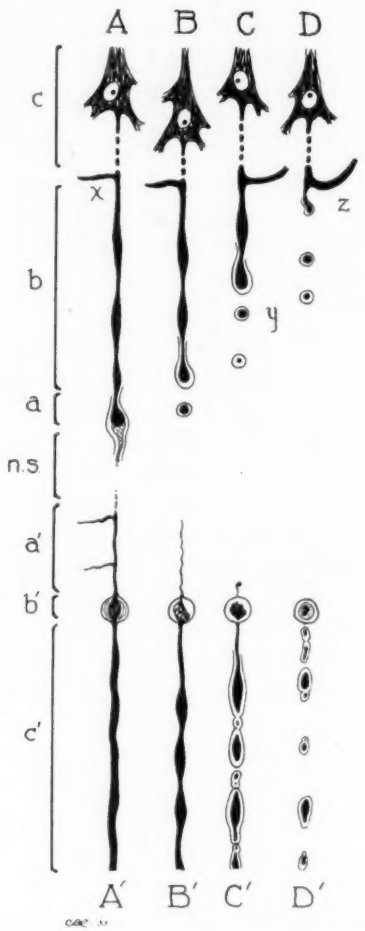

Fig. 2.—Changes in nerve fibers following experimental division just beneath the cortex, according to Cajal. *A* to *D* represent changes in the proximal segment at twenty-four hours and thereafter: *n.s.*, a necrotic segment; *a*, an end-bulb; *b*, a segment to the last collateral undergoing varicose change; *c*, a nerve cell and axon (the dotted portion indicates the portion of the axon from the cell to the last collateral); *x*, the last collateral; *y*, free balls consisting of separated end-bulbs, which are formed in turn from local varicosities; *z*, hypertrophy of the last collateral; *A'* to *D'*, represent changes in the distal segment (*A'*, from one to two days; *B'*, from two to three days; *C'* and *D'*, following days): *a'*, a terminal filament; *b'*, an end-bulb; *c'*, a degenerating distal segment.

or floating complicated glomeruli and arcs (fig. 1). The glomeruli, first seen along the fine tubes at the four hour interval, later formed typical varicosities.

In the coarser fibers sectioned in the white matter, two segments were again distinguished: a pale necrotic segment which broke down rapidly and a more persistent segment of traumatic degeneration. An hour after injury, the reaction in the axon was manifested by a club-like or ball-like thickening at the stump of the segment, surrounded by a clear "plasmatic chamber." After six hours, the terminal thickening was found to be accentuated and the hypertrophic segment demonstrated spiral or flexuous neurofibrillar bundles. Between eighteen and thirty-six hours, the process had so progressed that the segment just above the terminal bud or ball, which had been in a hypertrophic state, had in its distal portion undergone varicose alteration. This varicose segment was finally broken up into a series of balls which persisted in a free state for from three to ten days, ultimately undergoing resorption. At the end of the normal segment there was ultimately found a late retraction ball, which was more or less permanent. This was to be distinguished from the initial traumatic club forming at the distal end of the segment of traumatic degeneration in the first few hours after injury. This segment, therefore, was observed to undergo a retrograde degeneration in a centripetal direction to the last bifurcation or collateral of the axon arising in the white substance. Some of the larger axons underwent precocious destruction, after which large clear spheres which did not attract silver were found.

Interruption of Nerve Fibers in Gray Substance.—Section Below Collaterals: When nerve fibers were divided from their cells of origin by a section deep in the gray matter below the last collaterals, after twenty-four hours an elongated hypertrophic segment was found which extended to the last uninjured collaterals.[4] This hypertrophic segment ultimately degenerated, with the formation of retraction club (fig. 2). The lowermost collaterals became hypertrophic and were deeply impregnated with silver. According to Cajal's conception, the pyramidal cells with long axons had become transformed into those with short axons, the integrity of the uninjured collaterals being maintained to shunt the stimuli by way of other cortical cells in compensation for the interruption of their normal pathways. This seemed to be true particularly in very young animals. The hypertrophy of these collaterals was attributed to increased stimulation by the excess current passing over them.

4. Ramón y Cajal, S.: Alteraciones de la substancia gris provocados por conmoción y aplastamiento, Trab. d. lab. de invest. biol. Univ. de Madrid **9**:217, 1911.

Section Above the Collaterals: When the axons were sectioned near the cell body there was a notable absence of all manifestations of survival of the neurobions. Instead there was only slight local hypertrophy terminating in a point of corrosion. It was believed that the trauma which severed the fiber had resulted in the death of the cells, and that their morphologic identity had been maintained for the time being by preservation necrosis.

Section of Transverse Fibers of the Gray Matter: When a cut was made perpendicularly in the cortex, degenerative changes were found in the central ends of the fine transverse fibers.[4] These fibers consisted of the tangential axons of the cells of Martinotti, the terminal branches of corticifugal fibers and finally the collaterals of the pyramidal axons. The central stump of the fibers behaved in general in the same way as the central stump of the axons of the pyramidal cells, except that the terminal clubs were very small and that there was a small hypertrophic segment or none.

Comment.—It is of interest to note that Cajal's attention was directed primarily to a study of neuronal changes in the cerebellum.[5] In the main the changes in the nerve fibers were the same as those occurring in the cerebral hemispheres. As far as injuries to the human brain are concerned they are of less practical importance, for the cerebellum is less often injured.

While there can be no close comparison between the cleancut wounds in experimental animals and the more extensive and ragged wounds incident to injuries of the brain following accidents, it has been our purpose to trace, if possible, the changes in nerve fibers through the various time intervals. In order to do this, we have grouped the cases according to the length of the survival period and have studied the various changes characteristic of each interval. It was difficult to evaluate properly the shattering effect on nerve fibers of such injuries, but it may be assumed that they served merely to extend more or less the primary necrotic segments.

To those familiar with the extremely varied pathologic picture presented by injuries to the brain, with the multitude of different lesions resulting therefrom, it immediately becomes evident that nerve fibers may be interrupted in a number of ways. Petechial hemorrhages, small as they are, almost invariably result in an interruption of adjacent nerve fibers when once the escaped blood breaks through the confines of the perivascular space. Fibers may also be interrupted by irregular lacerations

5. Ramón y Cajal, S.: Note sur la dégénérescence traumatique des fibres nerveuses du cervelet et du cerveau, Trab. d. lab. de invest. biol. Univ. de Madrid **5**:105, 1907; Los fenómenos precoces de la degeneración neuronal en el cerebelo, ibid. **9**:1, 1911.

or softening consequent to diffuse bruising of the cortex. Nerve cells may be separated from their axons by a more or less extensive gross subcortical hemorrhage. Any lesion extending perpendicularly through the cortex will interrupt the fine transverse fibers. Local infarction of the white substance consequent to fat emboli likewise results in local interruption of nerve fibers. The finding of occasional isolated end-bulbs in groups of nerve fibers otherwise normal has suggested a possibility of rupture of such isolated fibers as the result of the shock of injury.

SOURCE OF MATERIAL AND METHODS OF STUDY

The material used for study in this investigation was taken from thirty-nine cases of fatal head injury, some of which have also been used in previous contributions of the series. The patients were in the wards of the Los Angeles County General Hospital or were seen by one of us (C. W. R.) in private practice. The material was forwarded to the Laboratory of Neuropathology through the courtesy of Drs. A. F. Wagner and John H. Schaefer of the Coroner's Department of Los Angeles County. The bodies were embalmed, usually within three or four hours after death. After removal from the skull the specimens were immersed in 10 per cent formaldehyde for further fixation. Blocks of tissue were taken from the brain in the region of the various gross lesions, or at times from areas grossly normal. The methods we have used in the study of nerve fiber change are: (*a*) Cajal's reduced silver method; (*b*) Bielschowsky's method for nerve fibers, and (*c*) the myelin sheath method (Courville-Krajian).

Gross Lesions of the Brain.—As the immediate consequence of accidents in civil life, certain fairly characteristic lesions of the brain are frequently observed. The influence of such lesions in the production of immediate or remote symptoms is a matter of clinical interest. One would be interested to know the ultimate effect on the clinical course in a given case of multiple petechial hemorrhages in the centrum ovale, of cortical contusions of various degrees and in various locations or of gross subcortical hemorrhage. It is recognized that a patient may survive any one or even several lesions of this type. Whether post-traumatic neuroses following head injuries, with their peculiar characteristics which often distinguish them from functional states following trauma to other parts of the body, are due to such gross lesions of the brain or to psychic trauma merits careful consideration. In other words, are so-called traumatic neuroses due to specific lesions in the brain, which makes these functional cases different from those of bodily injuries? The answer to this question is not likely to be obtained as the result of any single line of investigation. We feel, however, that a study of alterations in the nerve fibers, which are the conduction elements consequent to injury, may give some clues to the ultimate solution of the problem.

The function of many cortical areas and of certain association and commissural bundles is still not entirely clear. To assume that such cortical areas have no function simply because one is ignorant of it is to transgress a fundamental law of scientific investigation. Among the wide expanses of cortex whose function is largely unknown are those of the temporal lobes and the basilar surfaces of the frontal lobes, which are frequently altered by traumatic contusions. Furthermore, the frequent occurrence of hemorrhages in the centrum ovale, with interruption of numbers of nerve fibers at the site of the extravasation, not unlikely has an effect on the normal functioning of the brain. It has seemed to us that the first

step in the solution of the problem from a morphologic standpoint is a study of the results of these various lesions on the nerve fibers.

In a series of thirty-nine cases we have classified the gross lesions discovered at autopsy in the following manner: (1) cerebral compression, as by extradural and subdural clot; (2) diffuse subdural hemorrhage; (3) diffuse or patchy subarachnoid hemorrhage; (4) minor, moderate or severe contusions; (5) gross intracerebral hemorrhage, and (6) petechial hemorrhages.

It is obvious that local cerebral compression or subdural and subarachnoid hemorrhage can have no morphologically demonstrable effect on nerve fibers, and consequently such conditions have not been included in the present discussion.

MINOR CORTICAL CONTUSIONS

In this group of cases (table 1) we are concerned with the changes in the subcortical and cortical nerve fibers consequent to minor cortical contusions. We include in this group the small, apical, dished-out lesion of the crests of the injured

TABLE 1.—*Minor Contusion*

Case	Age, Years	Sex	Survival Period	Fixation Period	Location of Lesion
1	65	F	1¼ hours	Within 1 hour	Minor cortical contusion of dorsolateral surface of right temporal lobe
5	38	M	6¾ hours	1½ hours	Minor cortical contusion of basilar surface of right temporal lobe
11	9	F	26 hours	1½ hours	Minor contusion of cerebellar cortex
27	9	M	2 days	3 hours	Minor cortical contusion of dorsolateral surface of left parietal lobe
4	51	M	51 hours	3½ hours	Minor cortical contusion of right frontal operculum
30	62	M	79 hours	2½ hours	Minor cortical contusion of dorsolateral surface of right temporal lobe
6	26	M	91 hours	3 hours	Minor cortical contusion of dorsolateral surface of left frontal lobe

convolutions, usually surmounted with a small circumscribed blood clot or a large number of discrete miliary hemorrhages which result in disintegration of the superficial layers of the cortex. On cross-section, if one excludes the associated satellite hemorrhages which are usually found in the subjacent white substance, such a contusion is confined to the cortical gray matter. Within the group are found variations from small focal cortical extravasations to gross loss of cortical substance with rupture of the overlying leptomeninges. This type of lesion undoubtedly occurs in the brains of many persons who survive head injury.

In case 1 (survival period, one and one-half hours) the nerve fibers were studied in the white matter below a minor cortical contusion of the right temporal lobe and about the underlying satellite hemorrhages. Actual end-bulbs could not be distinguished with certainty, but varicose swellings of the injured fibers were already present. These varicosities were more often present in the smaller fibers than in those of larger diameter. Considerable twisting of the smaller fibers was also common. The terminations of nerve fibers traced into the hemorrhagic foci seemed to be in the form of "corrosion points" in which the nerve fiber tapered off to a point, at the apex of which granules indicating degeneration in the adjacent portion of the nerve fiber were seen. The nerve fibers stained deeply, presumably as a result of preservation necrosis. Varicosities could not be found

in the fibers traceable any distance from the local wound, but seemed to occur almost exclusively in regions comparatively distant from it, probably in fibers undergoing degeneration.

The radiating corticifugal fibers gave evidence of acute degeneration (fig. 3). This degeneration was characterized by fragmentation, fusion, central necrosis and rupture and dislocation of the axis-cylinders.

The radiating cortical fibers in the vicinity of a contusion of the temporal lobe had undergone changes similar to those found in the subcortical white matter. Many of these fibers had undergone preservation necrosis, particularly those in

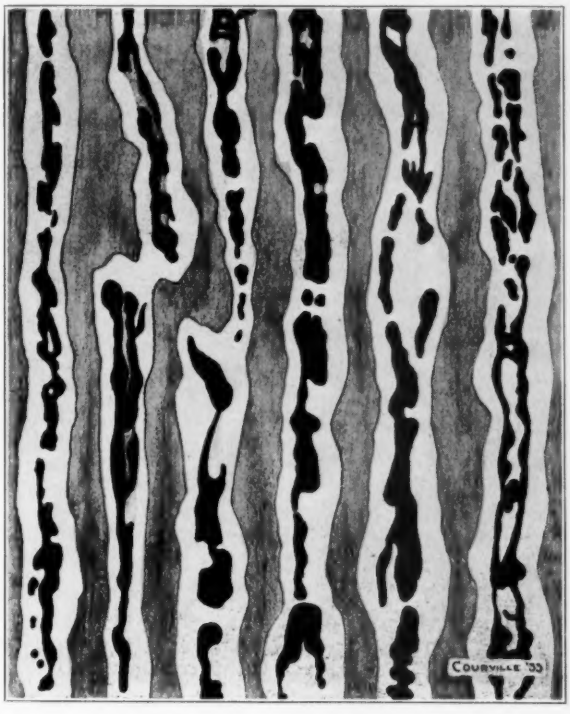

Fig. 3 (case 5; survival period, six and three-fourths hours).—Drawing from a reduced silver preparation, showing the manner of fragmentation in nerve fibers descending from the contused cortex.

the immediate vicinity of the hemorrhages and in the separated fragments of brain tissue. Marked corkscrew twistings and acute fragmentation were characteristically observed in these fibers.

In the immediate vicinity of the wound the superficial transverse fibers could scarcely be distinguished, and, judging from the extensive granulation, active degeneration of these fibers had evidently taken place. A few fragmented fibers remained, being less numerous as one approached the margin of the wound. The remaining fibers showed marked tortuosity, and zigzag fibers were still distinguishable in spite of poor impregnation, particularly in the region of the wound. The transverse fibers running into the wound were found to have undergone extensive degenerative changes in the form of varicosities and fragmentation.

In case 5 (survival period, six and one-half hours), in which there was minor bruising of the right temporal lobe, the nerve fibers in the subcortical white substance running into the bruised area and its satellite hemorrhages showed marked twisting in their terminal portions. These irregularities were sometimes so pronounced as to give rise to zigzag figures. End-bulbs were not numerous but were present and fairly typical. Where two or three of these twisted fibers lay in close proximity they gave rise to peculiar loops and spirals. In the vicinity of the contusion the tissue was filled with black granules, evidently due to active regressive change in the nerve fibers. In a smaller and more superficial cortical contusion in the right parietal lobe, an unusual appearance of degeneration occurred. Because of the diffuse character of the wound, if one was present, end-bulbs could not be discovered on these transverse fibers. Occasional varicosities were observed in the regions adjacent to grossly normal brain tissue.

In case 11 (survival period, twenty-six hours), the nerve fibers in the region of a minor contusion of the cerebellar cortex were studied. In the region of the extravasation of red blood cells the interrupted corticifugal fibers terminated in end-bulbs, hypertrophies and rings. The portion of the fiber adjacent to the end-bulb frequently showed hypertrophic and varicose segments characteristic of those found in Cajal's experimental injuries.[5] These fibers, apparently the proximal fragments and still attached to their cells of origin, are to be compared with those associated with the deep cortical incisions in Cajal's experimental animals. The fibers cut off from their cells of origin and all fibers in the vicinity of the hemorrhage assumed a typical "burnt string" appearance.

In case 27 (survival period, two days), in the region of a minor contusion of the left parietal lobe, preservation necrosis of the nerve fibers was evidenced by their attraction for reduced silver. Characteristic end-bulbs were found but were not particularly numerous. In this case the ends of the nerve fibers seemed to be lost in the focal hemorrhages. End-bulbs were more clearly distinguished at some distance below these extravasations, apparently on the larger nerve fibers. The nerve fibers in this region were undergoing hypertrophy, varicose change and fragmentation. The intracortical nerve fibers in the regions of the bruised areas were deeply impregnated, evidently having undergone preservation necrosis, a change again most strikingly observed in the region of the hemorrhages. This was also true of the fine superficial transverse cortical fibers immediately adjacent to the contusion. At a somewhat greater distance these fibers were less clearly demonstrated, and many of them had undergone fragmentation. An increase in their tortuosity was characteristic.

A man, aged 51, survived an injury for two days and three hours (case 4). At autopsy two distinct lesions were found. There was a recent minor cortical contusion in the opercular gyrus of the right frontal lobe as well as an old cystic cavity which was the result of a head injury sustained seven months previously. About the minor cortical contusion was found characteristic preservation necrosis (fig. 4), in addition to typical end-bulb formation and nerve fiber degeneration.

In case 30 (survival period, two days and seven hours), in the subcortical white substance beneath a superficial minor cortical contusion of the right temporal lobe numerous large end-bulbs were found. The persistence of the end-bulbs after this survival period indicates that they occurred at the terminal ends of fibers entering the cortex. In the same area there were many nerve fibers which were undergoing advanced degenerative change. In these fibers the situation of the axis-cylinders was indicated by rows of irregular fragments and granules. On either side of

this region fibers running into the undamaged cortex had a more normal appearance and stood out in marked contrast to those undergoing regressive change. In the injured cortex the smaller transverse fibers showed fairly characteristic hypertrophies, varicosities, terminal end-bulbs and rings.

In case 6 (survival period, three days and nineteen hours), in which there was a minor cortical contusion of the left inferior frontal gyrus, the nerve fibers in the region of the contusion showed a wide variety of forms of very large end-bulbs associated with local hypertrophies and varicosities. The nerve fibers whose cells of origin had been destroyed in the cortical contusion were found to

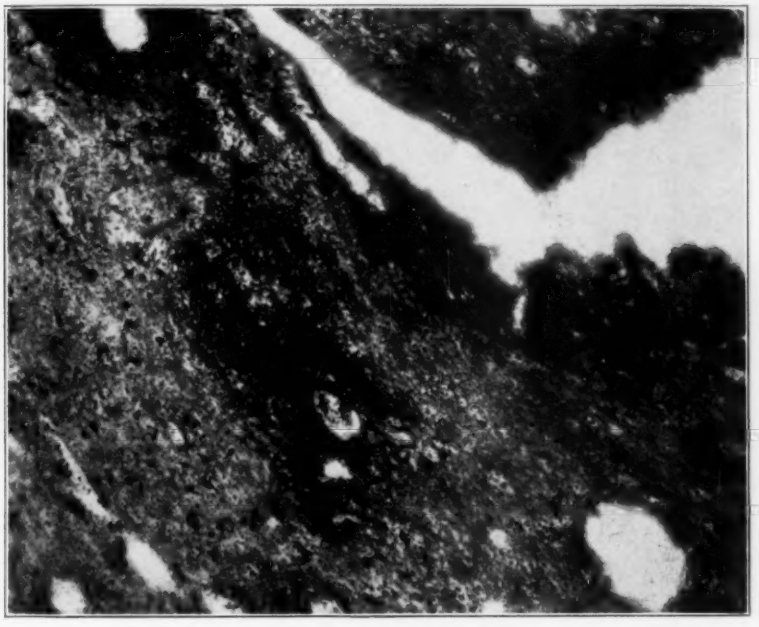

Fig. 4 (case 4; survival period, fifty-one hours).—A dark zone about a subcortical hemorrhage incident to preservation necrosis and granular degeneration of adjacent nerve fibers. Cajal's reduced silver method; × 100.

be undergoing extensive degenerative change. Complex, bizarre end-bulbs were isolated by the generation of the nerve fiber, or the latter was attached to them in the form of tail-like rows of disappearing granules. Some of the better preserved fibers retained an advanced "burnt string" appearance. Similar to the forms described by Cajal in experimental injury were the single and double varicosities situated at varying distances below the end-bulbs in the course of the degenerating fibers.

The size of the end-bulbs is proportional to the diameter of the nerve fiber. In their bizarre and multiform appearance these end-bulbs surpass even the curious forms described by Cajal. Their complexity beggars description. An attempt has been made to illustrate some of the more common and characteristic forms in the accompanying drawings (figs. 5 and 6). The end-bulbs on the distal segment may be classified as follows: (1) very large bulbs with multiple terminal loops;

(2) moderately sized bulbs (*a*) with lateral or terminal loops, (*b*) with fusiform terminations or (*c*) with blunt-tipped masses of granules; (3) narrow bulbs, (*a*) with spear head or halberd forms, (*b*) with blunt-tipped bulbs, (*c*) with irregular nodular thickenings or (*d*) of the torch flame type; (4) small terminal spirals or rings. It is likely that these complex forms are due to regressive changes taking place in the retracted, swollen and fused, or separated neurobions, as Cajal suggested.

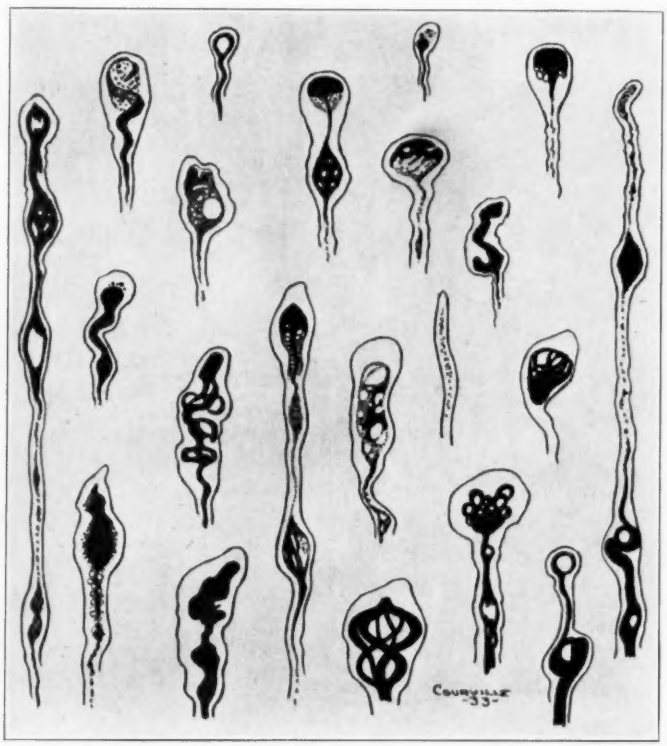

Fig. 5 (case 6; survival period, ninety-one hours).—Subcortical interruption of nerve fibers. Complex end-bulbs and rings are formed on the termination of the distal segment. Cajal's reduced silver method.

MODERATE CORTICAL CONTUSIONS

In this group of lesions are included contusions of greater magnitude and depth than those described in the previous section. These contusions involve more of the exposed cortex and extend wedgelike into the underlying white substance. There is usually some loss of cortical tissue, and the overlying pia-arachnoid is invariably torn. On cross-section these lesions have a tendency to be wedge-shaped, as compared with the more frequently crescentic outline of the minor cortical contusions. They are characteristically found on the basilar or dorsolateral surface of the temporal lobes or on the basilar surface of the frontal lobes. Table 2 lists the moderate cortical contusions observed in the series of cases under consideration, together with the survival period. It is our purpose in

dividing contusions into minor and moderate groups to note particularly whether or not the extent of the lesion influenced the time of the appearance of end-bulbs. This group of lesions is of interest because it represents a type of lesion that is frequently curable.

In case 19, a woman, aged 70, was killed outright. The nerve fibers in a narrow zone about the lesion had undergone fragmentation, but, as was suspected, there was no evidence of reaction in the more distant fibers. In case 17, that of a woman, aged 84, who died one and a quarter hours after injury, no evidence of

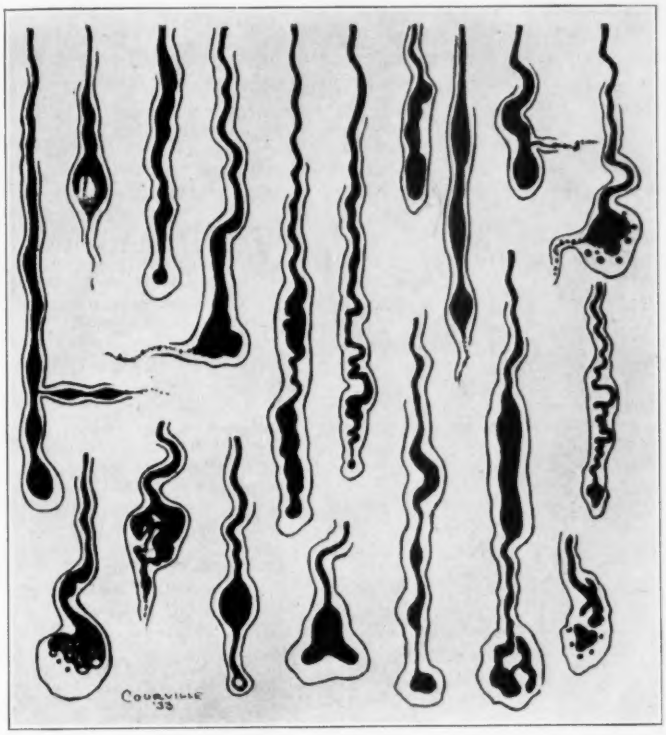

Fig. 6 (case 6; survival period, ninety-one hours).—Subcortical interruption of nerve fibers, showing the types of end-bulbs formed at the end of the proximal segment. Hypertrophied and varicose segments are also shown. The collaterals are undergoing degeneration or varicose alteration. Cajal's reduced silver method.

end-bulb formation was observed. In case 14, that of a woman, aged 75, who died two hours after injury, there were small end-bulbs and rings in the cortex near the bruised area. The nerve fibers adjacent to the injury gave immutable evidence of the formation of small fusiform hypertrophies.

In case 23 (survival period, twelve hours), following a moderate cortical contusion of the left temporal lobe numerous typical end-bulbs were found on nerve fibers radiating into the cerebral cortex. The nerve fibers leaving the cortex were already undergoing an advanced degree of degeneration, characterized by fragmentation and granulation. End-bulbs were found some distance below the

contused cortex, as has already been described in the case of minor contusions. The nerve fibers in the region of the cortical and subcortical hemorrhage showed a marked degree of preservation. These observations seem to lend strength to Cajal's conception that there are substances in the extravasated blood which preserve the fibers from immediate disintegration.

In case 21, that of a girl, aged 17, who survived an injury for fifty-six hours, there was a moderate cortical and subcortical contusion of the left temporal lobe. Within the cortex numerous small end-bulbs and rings were found on both the transverse and the vertical fine fibers. In the underlying white matter numerous well formed end-bulbs and rings were observed. These end-bulbs were found on both the vertical and the subcortical association fibers. In the case of a man who survived a fairly extensive contusion of the right temporal lobe for seven and a half days (case 37) end-bulbs were found about the areas of hemorrhage and degeneration. These seemed to be less numerous than in cases with a shorter survival period.

TABLE 2.—*Moderate Cortical Contusions*

Case	Age, Years	Sex	Survival Period	Fixation Period	Location of Lesion
19	70	F	Killed outright	Within 30 minutes	Moderate cortical contusion of dorsolateral surface of right temporal lobe
17	84	F	1¼ hours	2 hours	Moderate cortical contusion of basilar surface of right frontal lobe
14	75	F	2 hours	3½ hours	Moderate cortical contusion of left hippocampal gyrus
23	30?	M	12 hours	9 hours	Moderate cortical contusion of dorsolateral surface of left temporal lobe
21	17	F	56 hours	10 hours	Moderate cortical contusion of dorsolateral surface of left temporal lobe
37	44	M	7½ days	2¼ hours	Moderate cortical contusion of basilar surface of right frontal lobe
9	32	M	14 days	4 hours	Moderate cortical contusion of dorsolateral surface of left frontal lobe
38	26	M	15 days	1¾ hours	Moderate cortical contusion of basilar surface of right frontal lobe
25	38	M	21 days	3½ hours	Moderate cortical contusion of dorsolateral surface of right temporal lobe

In case 9, nerve fibers in the region of a fourteen day old contusion of the dorsolateral surface of the left frontal lobe showed numerous hypertrophied portions and varicosities. Characteristic end-bulbs were also present in considerable numbers (fig. 7). The interval between injury and death had permitted the accumulation of large numbers of phagocytes in the contused areas. With the reduced silver method these phagocytes were found to contain small end-bulbs, convoluted and distorted portions, varicose segments of the smaller nerve fibers, large irregular fragments of the larger fibers and, finally, more or less numerous small granular fragments of more completely disintegrated neurobions. It seems evident from this observation that once active phagocytosis takes place the nerve fibers may be engulfed before complete disintegration occurs. The nerve fibers in the regional cortex were found to be hypertrophied and to have a granular appearance characteristic of the "burnt string" type of regressive change.

In case 38 (survival period, fifteen days) the apex of the contused area was marked with a fine, dustlike precipitate, evidently the remains of degenerated nerve fibers. Throughout this area there was absence of formed fibrillar structures and therefore of end-bulbs. It seems evident that a more or less complete

disintegration of the damaged nerve fibers had taken place. In the adjacent cortex, likewise, the formed structures were obscured by a cloud of fine black granular precipitate. In case 25, that of a man, aged 38, who survived a head injury for three weeks, there was found an elongated moderate contusion of the right temporal lobe. The contusion extended into the underlying white substance of the convolution and was in this sense a transitional form between a moderate and a severe lesion. The nerve fibers for some reason were poorly impregnated throughout the section. More peripherally, however, they were better demonstrated. The adjacent

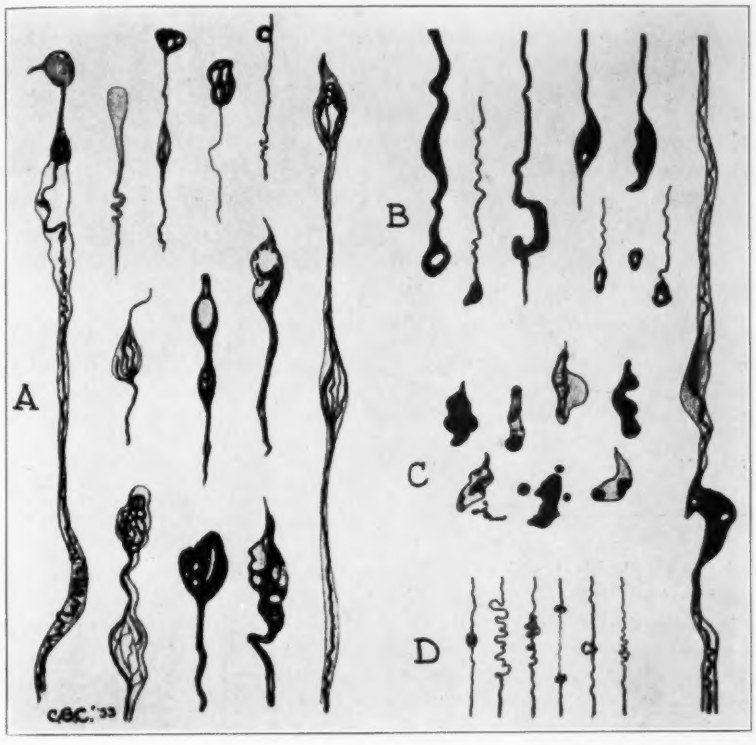

Fig. 7.—Distal and proximal end-bulbs and changes in the nerve fibers shown by Bielschowsky's method: *A* (case 4; survival period, fifty-one hours) shows end-bulbs and changes in the distal segments of the nerve fibers below a minor cortical contusion. *B* (case 9; survival period, fifteen days) shows end-bulbs and changes in the proximal segments of the nerve fibers at the margin of a cortical contusion. *C* (case 4) shows end-bulbs separated from degenerating nerve fibers. *D* (case 3; survival period, two hours) shows twists and convolutions in fine cortical nerve fibers.

fibers were found under higher magnification still to be undergoing degenerative change, manifested by rows of dark granules along the margin of the defect. In this area end-bulbs were also found. As in case 9, there was a very active proliferation of phagocytes, which again contained remains of nerve fibers. The phagocytic cells within an incomplete connective tissue wall of the defect contained a peripheral border of fine black granules, evidently the remains of degenerated

neurobions. Outside the connective tissue wall, the site of collections of débris, where, peculiarly, end-bulbs and degenerating nerve fibers could still be found, the phagocytes contained larger fragments of axis-cylinders.

SEVERE CORTICAL AND SUBCORTICAL CONTUSIONS AND LACERATIONS

Severe contusions or contused lacerations of the brain may be defined as extensive bruisings of the cortex, including several adjacent convolutions, which involve to a considerable degree the underlying white substance. It is this type of lesion which is seldom recovered from and in many cases is probably the cause of death in patients surviving an injury for from a few hours to two or three days. It may be questioned whether this refinement of classification is practical, particularly when it is appreciated that in ordinary histologic examinations only a small block of tissue from the margin of the lesion can be studied. The lesion differs from the minor or moderate contusions in the width of the zone of degeneration about the actual defect. This type of lesion perhaps is better defined as a contused laceration, because the hemorrhage from the larger subcortical

TABLE 3.—*Severe Cortical and Subcortical Contusions and Lacerations*

Case	Age, Years	Sex	Survival Period	Fixation Period	Location of Lesion
26	35	M	15 hours	5 hours	Contusion of dorsolateral surface of left temporal lobe
11	9	F	26 hours	1½ hours	Contusion of dorsolateral surface of left temporal lobe
7	14	M	38 days	2 hours	Contused laceration of left temporoparietal region

vessels is so abundant and of such sudden onset that it becomes a destroying element and not infrequently hollows out the involved frontal or temporal lobe. We have also included rather arbitrarily an extensive laceration of the brain due to indriven fragments of a compound, comminuted fracture of the skull (case 7). Under ordinary circumstances it would probably be best to indicate the latter type of lesion as the true laceration. The three cases here described are included in table 3.

In case 26, that of a man, aged 35, who survived an injury for fifteen hours, the nerve fibers running into the contused areas or into hemorrhagic foci showed numerous and well marked hypertrophic segments, varicosities and end-bulbs. These end-bulbs were particularly abundant adjacent to the large cavity occupying the central portion of the temporal lobe. In a girl, aged 9 (case 11), who died twenty-six hours after a fall to the pavement, a severe contusion of the entire left temporal lobe was found at autopsy. The nerve fibers in the white substance in the region of the superficial contusion revealed a patch of degeneration manifested by imperfect impregnation, fragmentation or granulation. Numerous end-bulbs, focal hypertrophies and varicosities were found (fig. 8). Adjacent to the bruised area, the injured tissue was again found to be marked by clouds of fine black granules, and in regions about focal hemorrhage by preservation necrosis of the nerve fibers. Otherwise, as one approached the contused area all evidence of fibers disappeared. Under higher magnification it was found that the nerve fibers entering the damaged cortex in the immediate region of the contusion had under-

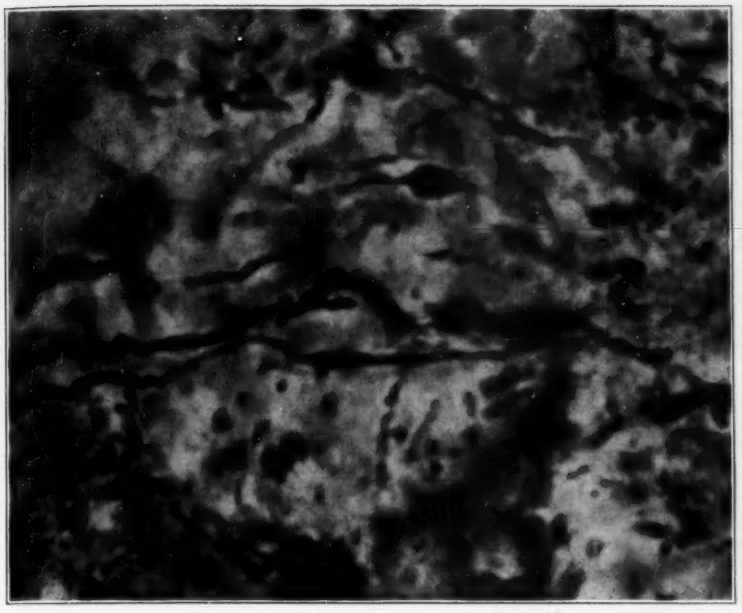

Fig. 8 (case 11; survival period, twenty-six hours).—Hypertrophied and varicose segments and small end-bulbs in the tangential fibers of the molecular layers of the cerebral cortex adjacent to a contusion. Cajal's reduced silver method; ×2,800.

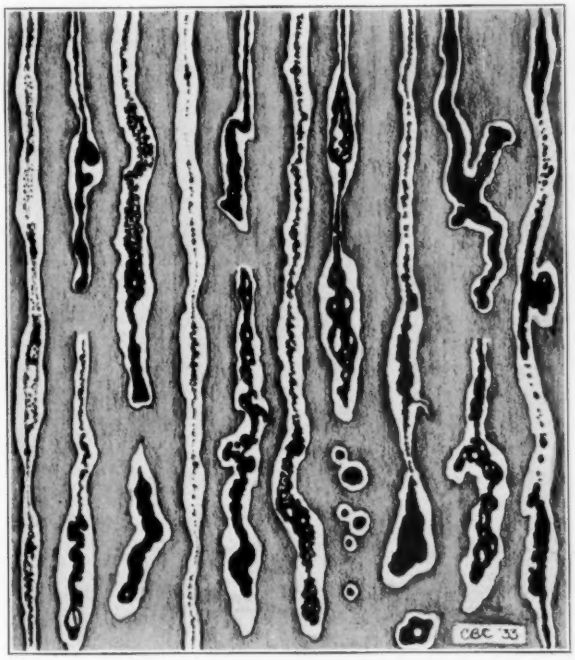

Fig. 9 (case 7; survival period, thirty-eight days).—Drawing from a reduced silver preparation, showing types of degeneration in nerve fibers adjacent to a severe cortical and subcortical laceration (granular, vacuolar, fragmentary, "burnt string," etc.). End-bulbs, balls and rings are also shown.

gone fine granulation, while somewhat more distinct strands or fragments of nerve fibers remained. In some of these entering cortical fibers more distant from the seriously damaged cortex, the "burnt string" type of degeneration was present. It is important in this case also to note the occurrence of extensive regressive changes and end-bulb formation in the white substance at quite a distance from the contused cortex. This represented areas in the middle of the temporal lobe.

Case 7 is unique in this series in that it was the only one showing extensive and deep laceration of the brain by indriven fragments of the skull. The patient, a boy, aged 14, died of exhaustion after thirty-eight days. At necropsy there was found an extensive disorganization of the brain in the left temporoparietal region, with adhesions to the dura and an enlargement of the adjacent lateral ventricle consequent to the loss of tissue. The local pathologic process was characteristic both in the irregular and diffuse nature of the injury and in the formation of a heavy connective tissue scar. The nerve fibers were poorly impregnated for a considerable distance from the connective tissue margin of the wound. The transverse fibers in the cortex near the margin of the wound showed characteristic hypertrophies, varicosities and peculiarly formed end-bulbs. The small fibers showed marked twisting and looping. There were no visible cells in the cortex in this region, and the vertical fibers had disappeared. Transverse fibers still remained in various stages of disintegration. In the somewhat more distant cortex the transversely placed fibers still showed end-bulbs and varicosities. In the white substance at a greater distance, several millimeters from the wound margin, peculiar regressive changes in the nerve fibers characterized by macelike swellings, fusiform granular enlargements and "burnt string" degeneration were observed (fig. 9). The terminations of the fibers were frequently characterized by triangular swellings attached by their apexes to the nerve fibers still capable of being impregnated.

INTRACEREBRAL HEMORRHAGE

As previously stated, in traumatic injuries of the human brain it has been difficult to find conditions which might be taken as counterparts of Cajal's experimental lesions. However, there is a closer analogy between gross subcortical hemorrhage which separates the cortex from the underlying nerve fibers and the deep cortical or subcortical incisions in Cajal's experimental animals. The extent of the hemorrhage usually results in the separation of a greater or lesser area of cortex, and it has been interesting to note the effect of this type of injury on the cortical nerve cells and the remains of the axis-cylinder. Table 4 contains a list of the cases of this type of lesion in the series. We have included from a technical standpoint some smaller subcortical hemorrhages (cases 22 [table 5], 30 and 38) which have resulted in a limited separation of the cortex but have cut off the cortical fibers in a similar manner. Under ordinary circumstances these lesions would be classed as rather large focal hemorrhages. We have not included the severe contused lacerations often associated with extensive cortical hemorrhage, for in these cases, except in the immediate vicinity of the defect, there is almost invariably a zone of white substance which remains attached to the cortex. A considerable portion of the axon necessarily remains intact.

One of the cases of the series proved to be of great interest in that the patient survived the first injury for seven months (case 4) only to succumb to a second injury after fifty-one hours. It is evident, therefore, that such a lesion may be survived. On the basis of our figures, four of the five patients with severe intracerebral hemorrhages died within five days of the injury. Since this is the case, it is of special interest to study the histologic alterations in the nerve cells and fibers in the cortex over the lesion.

In the case with the shortest survival period (case 36), that of a girl, aged 6½ years, who died four and a half hours after the injury, a massive hemorrhage was found in the left temporal lobe. Microscopically, there was a layer of white substance as well as of cortex which formed the shell of the hemorrhagic cavity. The axons from the overlying nerve cells revealed numerous hypertrophies, varicosities and end-bulbs. These elements were also present in the fibers which were tangential to the margin of the cavity.

A man, aged 21, died thirty-one hours after injuries sustained in an automobile collision (case 2). At autopsy a hemorrhagic cavity was found in the posterior portion of the left temporal lobe. The blood clot which recently occupied this cavity had broken through into the subarachnoid space at the base. The somewhat contused cortex which separated the cavity from the subarachnoid space revealed characteristic balls, end-bulbs and hypertrophied and varicose segments, which in some instances extended proximal to the lowest remaining collateral. The remaining narrow zone of subcortical white substance showed definite changes in the

TABLE 4.—*Intracerebral Hemorrhage*

Case	Age, Years	Sex	Survival Period	Fixation Period	Location of Lesion
36	6½	F	4½ hours	3½ hours	Massive hemorrhage into left temporal lobe
2	21	M	31 hours	4-5 hours	Massive hemorrhage into left temporo-occipital region
30	62	M	79 hours	2½ hours	Small hemorrhage into right external capsule
20	46	M	5 days	7 hours	Massive hemorrhage into left temporal lobe
38	26	M	15 days	1¾ hours	Small hemorrhage into right frontal lobe
4	51	M	7 months	3½ hours	Massive hemorrhage into right temporo-occipital region

transverse fibers as well. The outstanding characteristic in this case was the marked tortuosity, twisting and complexity of the neurobion pattern. Knots of twisted fibrils formed end-bulbs and irregular masses in their course. The presence of fusiform swellings in the same field seems to verify Cajal's conception that these swellings are due to fusion of the corkscrew formations of the neurobions.

In case 30, which was similar in local detail to case 36, after a survival period of three days and seven hours, numerous end-bulbs were found on the axons running to the margin of the hemorrhagic cavity. These end-bulbs displayed an unusual variety of appearances and were associated with hypertrophies and varicosities for a considerable distance. Similar but smaller end-bulbs were found on the transverse fibers of the subcortical white substance.

In case 20 (survival period, five days), in which a massive hemorrhage was found in the left temporal lobe, the neurobions in the immediate vicinity of the margin of the cavity failed to be well impregnated. This was due to granular degeneration of the axis-cylinders of the transverse fibers. End-bulbs still persisted in these ruptured transverse fibers, but stood out more clearly, owing to the degeneration of the remaining nerve fibers. There were a number of end-bulbs on the corticifugal fibers found in the white substance, apparently near the cortical margins. Bulbs, local hypertrophies and varicose segments were also observed.

In case 38 (survival period, fifteen days), a small subcortical hemorrhage in the right frontal lobe was found to be surrounded by a narrow zone of softening in which active phagocytosis was taking place. The situation differed in that there was a greater distance between the outer margin of the hemorrhage and the cortex, varying from 1 to 3 cm. The margin of the hemorrhagic area toward the cortex revealed numerous various sized end-bulbs, with adjoining hypertrophic and varicose segments. In the débris at the margin of the preserved tissue, free end-bulbs, balls and even portions of the hypertrophic segments could be seen. Many of the phagocytes were laden with black granules or short segments of nerve fibers.

In case 4 autopsy revealed an old hemorrhagic cavity in the right temporo-occipital region, presumably dating from an injury received seven months before death. Examination of the cortex overlying the hemorrhagic cavity revealed end-bulbs on the axon extending to within a very short distance of the cell itself. This was due to the fact that the margin of the hemorrhagic cavity extended nearer the cortex. Two types of axons should be described. Here and there were found long axons of fine caliber having a somewhat twisted and convoluted course and marked by terminal end-bulbs preceded by a short hypertrophic segment. In the other group there were changes in a short axis-cylinder which extended up to or beyond the last collateral. These fibers terminated in end-bulbs or mace-like swellings, usually with a small thread extending therefrom. The remainder of the axon was either normal in size and marked with occasional vacuoles or slightly swollen and granular, in which case there was almost invariably a swelling at the point of separation of the last collateral. This segment of axon was at times diffusely hypertrophied, tortuous and intensely impregnated. In the cortex numerous end-bulbs were also found, at times in clusters suggesting swelling of dendritic terminations. Many of the nerve fibers in the cortex resembled a typical "burnt string" degeneration.

PETECHIAL HEMORRHAGE

Petechial hemorrhages, aside from those found as satellite foci about cortical contusions, have been of considerable interest to us as a possible cause of post-traumatic symptoms. As will be shown, a petechial hemorrhage first fills the perivascular space of Virchow and Robin. If it is large, it breaks through the boundaries of this space and results in the interruption of the nerve fibers in all directions in the immediate vicinity. As such hemorrhages not infrequently occur in the corpus callosum, where the fibers are closely packed, it is not difficult to see how transmission of nerve impulses from one hemisphere to another would be seriously interfered with. Furthermore, petechial hemorrhages are not uncommonly observed in the white substance of the frontal lobes, and it is not unreasonable to assume that interruption of such pathways might be responsible for the neurotic manifestations commonly observed in posttraumatic states. The occurrence of these hemorrhagic foci in the pons or cerebellar peduncles may result in more serious consequences; in fact, some authors attribute serious symptoms resulting in death to such focal hemorrhages in the brain stem.

One interesting group of cases is comprised of those in which multiple petechial hemorrhages due to fat emboli are found throughout the centrum ovale. These cases are not to be technically included with those of traumatic injury of the brain. However, such lesions may follow fractures of traumatization of long bones by which globules of fat are set free in the circulation. The group of cases in which petechial hemorrhages of one variety or another were found are listed in

table 5. Petechial hemorrhages may have been found in many other locations, but only the particular areas studied in this connection are indicated in the table.

In the case of a woman, aged 70, who was probably killed immediately (case 19), petechial hemorrhages were found in the white substance of the right parietal lobe. Microscopically, these hemorrhages were confined to the perivascular spaces or the immediately adjoining area. In this region fragmentation of the nerve fibers was observed. Some of them also revealed fusiform or sausage-shaped swellings in their course. No end-bulbs were found in the larger fibers, and none could be made out with certainty in the smaller ones. Corkscrew twistings of the local fibers often gave rise to the impression that small end-bulbs were present.

In the case of a man, aged 41, who survived an injury for two hours (case 3), petechial hemorrhages were found in the white substance beneath a superficial contusion. Some local hypertrophy was observed in some of the adjacent nerve

TABLE 5.—*Petechial Hemorrhage*

Case	Age, Years	Sex	Survival Period	Fixation Period	Location of Lesion
19	70	F	Killed	½ hour	Right parietal centrum
3	41	M	2 hours	3 hours	White substance of right frontal lobe
5	38	M	6¾ hours	1½ hours	Pons
23	30	M	12 hours	9 hours	Pons
10	35	M	14 hours	3½ hours	White substance of left superior parietal lobule
26	35	M	16 hours	5 hours	Middle cerebellar peduncle
21	17	F	56 hours	10 hours	Right hippocampus
6	26	M	91 hours	3 hours	White substance of left frontal lobe
8	22	M	4½ days	2 hours	White substance of right and left cerebral hemispheres (fat embolism)
22	38	M	6½ days	4½ hours	White substance of left parietal lobe

fibers, together with an increased tortuosity. No well formed end-bulbs were found in the larger fibers. However, under a high magnification small bulbs were occasionally seen at the ends of interrupted fine fibers. At the ends of some of the larger fibers evidence of early bulb formation was indicated by fusiform swelling, often with a terminal filament. This observation would suggest that end-bulb formation in human beings has its beginning between one and two hours after injury in both the small and the large fibers, and that the location for such changes is subterminal, the distal filament corresponding to the remains of Cajal's necrotic segment. This was also shown in case 14, in which small end-bulbs were found on the fine nerve fibers two hours after injury. These occurred about a small subcortical satellite hemorrhage (fig. 10).

In the pons of a man, aged 38, who survived an injury for six and three-quarters hours (case 5), atypical end-bulbs or clublike swellings were observed at the ends of interrupted nerve fibers. In these areas hypertrophied segments of nerve fibers were also seen, associated with local tortuosities and corkscrew twistings. However, such changes were considerably less than one would expect to find elsewhere in the brain under similar circumstances.

In case 23, that of a man, aged 30, who survived an injury for twelve hours, there was found a comparatively large extravasation of blood in the upper part of the pons. Aside from what appeared to be preservation of the adjacent nerve fibers there was acute fragmentation of the nerve fibers in the involved

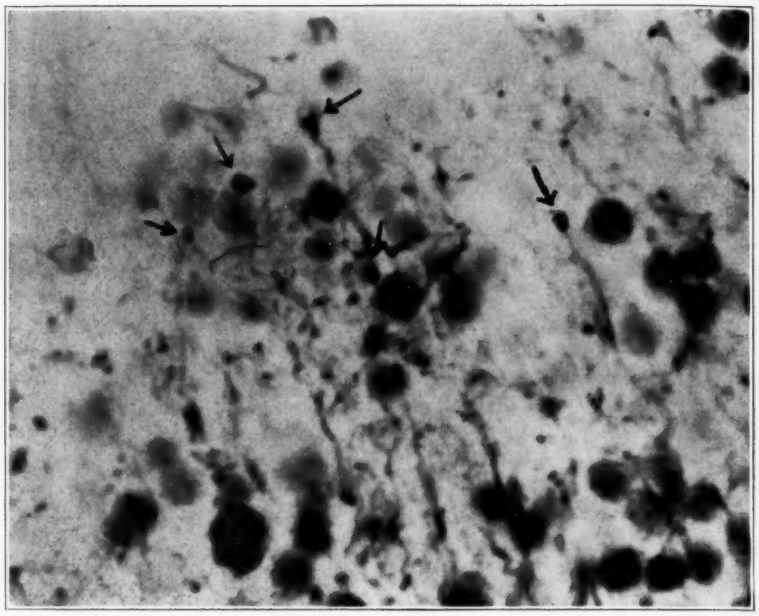

Fig. 10 (case 14).—Small end-bulbs at the termination of fine fibers two hours after injury in the region of a subcortical hemorrhage. Cajal's reduced silver method; × 1,400.

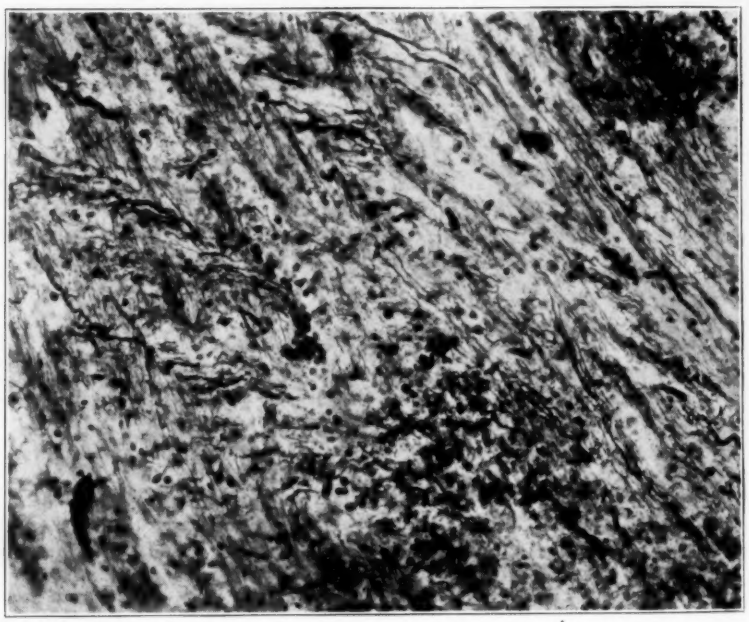

Fig. 11 (case 26; survival period, fifteen hours).—Large atypical end-bulbs and clublike terminations of nerve fibers in the middle cerebellar peduncle interrupted by local hemorrhage. Cajal's reduced silver method; × 280.

area. Some of the larger fibers also revealed atypical blunt terminations, not having formed characteristic end-bulbs. This seems to indicate that end-bulb formation in the large fibers of the pons is a much slower process than in the cerebral or cerebellar hemispheres.

Small petechial hemorrhages were found in the white substance of the left parietal lobe in the case of a man, aged 35, who survived an injury for fourteen hours (case 10). These were almost entirely ring hemorrhages confined to the perivascular spaces. Because of this fact there was a minimal interruption of adjacent nerve fibers as evidenced by the only occasional end-bulbs in their vicinity. One rather interesting observation was the occasional appearance of local hypertrophies and even of well formed end-bulbs at some distance from the vessels.

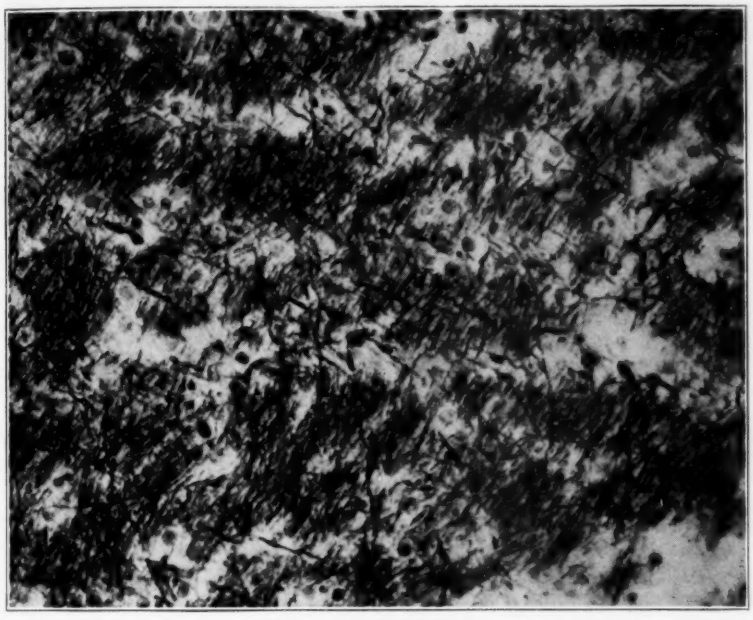

Fig. 12 (case 8; survival period, four and a half days).—End-bulbs, appearing like a school of fish, on nerve fibers interrupted by an infarcted area incident to fat embolism. The margin of the infarcted area is shown in the lower right hand corner. Cajal's reduced silver method; × 330.

In the case of a man, aged 35, who survived an injury for sixteen hours (case 26), petechial hemorrhages were found in the middle cerebellar peduncle. There was some hypertrophy of the local fibers. Atypical end-bulb formation was also observed (fig. 11). No large end-bulbs of characteristic appearance were seen. Perhaps one reason for this was the absence of intensive destruction by the hemorrhage which was inclined to infiltrate between the fibers rather than to accumulate in any given situation. One peculiarity was the occurrence of varicose or knotty swellings with occasional interruptions on the local fibers, together with granular and vacuolar degeneration which resembled the "burnt string" degeneration which was seen in the cerebral hemispheres about local injuries.

About a small focal hemorrhage into the stratum lucidum and the stratum radiatum of the right hippocampus in the case of a girl, aged 17, who survived an injury for fifty-six hours (case 21) various evidences of change in the nerve fibers were observed. In the fibers of the tangential fasciculus variously sized end-bulbs, hypertrophies and fusiform varicosities were found. The varicosities were evidently derived from local corkscrew twistings of the nerve fibers. End-bulbs were also found on the fine transverse intracortical fibers as well as on the larger vertical ones.

In the case of a man, aged 26 (case 6), with a survival period of three days and nineteen hours, many forms of end-bulbs were observed about small petechial hemorrhages in the white substance of the left frontal lobe. Some of these end-bulbs were very complex and revealed terminal filaments, rings, granules or more complex masses within the absorption chamber. Furthermore, almost invariably there was subterminal hypertrophy or varicosity, or peculiar multinodular masses were found. The interrupted fibers were divided either by the mass of the hemorrhage or by a lateral pressure resulting from it. This was indicated by the end-bulbs found coursing tangentially about the margin of the hemorrhage. These end-bulbs resembled closely the complex structures found in the subcortical hemorrhages previously illustrated (figs. 5 and 6).

A somewhat unusual and interesting situation existed in case 8. A man, aged 22, survived a fall for four and a half days, having sustained extensive fractures of the lower extremities. In spite of little evidence of external injury to the head, the patient remained comatose until the time of death. Histologic examination of the numerous petechial hemorrhages and small infarcted areas revealed them to be due to fat emboli. Sections impregnated with Cajal's method disclosed areas of extensive degeneration about these petechial hemorrhages, with interruption and fragmentation of the nerve fibers. All forms of end-bulbs, varicosities and hypertrophies were demonstrated (fig. 12). Other sections stained by myelin sheath methods and by Cajal's method indicated that the myelin swellings and the end-bulbs were not found in the same zones. This is somewhat at variance with Cajal's observation in experimental injury to the brain, in which it was believed that the end-bulbs were contained within the globular swellings of the myelin sheaths.

In case 22 (survival period, six and a half days), petechial hemorrhages were found in the subcortical white substance of the left parietal lobe. Characteristic end-bulbs as well as single or double fusiform varicosities and local hypertrophies were observed. The absorption chambers about the end-bulbs seemed to be larger than those in the previously studied cases.

COMMENT

Our observations in this series of cases seem to confirm those of Cajal on nerve changes in experimental injury to the brain. That any interruption of a nerve fiber is followed by more or less complex changes in the proximal and distal ends of the fiber is clearly established. It will be well to summarize briefly the results of our observations as to the structure and significance of the changes.

End-Bulbs.—It is evident that for a varying distance in either direction from the point of interruption of the nerve fiber immediate necrosis

occurs. This corresponds to Cajal's "necrotic segment." We have been unable to determine the exact character of the degeneration of this necrotic segment, largely because of a diffuse granulation in the irregular margin of the injured area. Regardless of the location of the interruption, a corrosion point is first formed, which is continuous with the row of granules, the remains of the necrotic segment. This corrosion segment can be made out on the larger fibers up to two hours after injury.

The first evidence of end-bulb formation is found approximately two hours after injury in the form of small fusiform or globular swellings on the fine fibers. For some unknown reason the smaller fibers maintain their integrity nearer to the margin of the wound than the larger ones. This holds true for a considerable time following injury, especially when the interruption occurs in the white matter. This proved also to be the case in Cajal's experimental incision, so it is evidently not dependent on the mode or type of injury. Between two and three hours after injury, local hypertrophy begins to take place, and by four hours typical end-bulbs can be found. After this period characteristic end-bulbs in considerable numbers may be found about subcortical or central interruptions.

The persistence of end-bulbs naturally depends on whether they are attached to the proximal or to the distal segment. On the distal segment their survival is limited. After the second day (case 4), free end-bulbs can be found owing to degeneration of the distal segment. Just how long they can persist in this situation is difficult to state, but it is questionable, judging from acute regressive changes as observed in the remainder of the distal portion, whether they are to be identified longer than a week after injury.

A different situation necessarily exists in the case of the end-bulb on the proximal segment. The behavior of these structures also differs from the standpoint of their proximity to the cell of origin. If the nerve fibers are interrupted just below the cortex as a result of subcortical hemorrhage, regressive changes take place toward the cell of origin. This process may go beyond the last collateral and extend within a short distance of the nerve cell itself. We have not been able to demonstrate in our material the logical sequence of events which Cajal described in his experimental animals. In case 4, in which there was a subcortical hemorrhage of seven months' standing, we found larger end-bulbs persisting on the remains of the shortened axons. After this period there was little evidence of local hypertrophy or varicosities, end-bulbs often being found attached to very thin nerve fibers. At the point of juncture of an axon with its collaterals, swellings were sometimes found. We were unable to find any evidence of hypertrophy of the collaterals such

as Cajal described. At times the end-bulbs persisted as intricate mace-like swellings.

Fibers entering a damaged area at a point relatively distant from the cells of origin may retain their end-bulbs for a considerable time. We found them in this series as late as seven months, and Penfield [6] found them in old scars many years after injury. In ragged, irregular wounds (as in case 7) the primary end-bulbs may be broken off, owing to secondary degenerative changes in the tissue which overlap the zone of primary reaction. In such instances rather complex reticulated or vacuolated end-bulbs of bizarre shape and outline and of unusually large size may be found. Subterminal fusiform granular swellings are often observed.

The significance of end-bulb formation is of interest. So far as the human brain is concerned, it seems that these structures are entirely degenerative, being the reaction of the injured neurobions. In favor of this conception is the observation that the end-bulbs on the distal segment are more complex and bizarre than those attached to the living segment. Therefore, size or complexity is not indicative of a response of living axis-cylinders. Their persistence without marked change for long periods suggests that they assume the nature of a scar on the end of these fibers. We were unable to find any changes suggestive of regeneration, such as Cajal described in his new-born or young experimental animals.

Degeneration in Nerve Fibers.—As there is no regeneration of nerve fibers of the brain, any interruption of these structures indicates a permanent loss of function of the fiber and, to a greater or lesser extent, of the cell from which it arises. Just what part this must play in the disturbance of brain function must of necessity depend on the severity of the injury, on the location of the injured areas and no doubt on the individual susceptibility of the patient. As would be suspected, interrupted nerve fibers undergo complete degeneration of the distal segment. This process begins within a few hours; by six hours there is active fragmentation of the axis-cylinders, which in the course of the next day or two show extensive change, and by the end of three weeks the argentophil material has largely disappeared.

Cajal described at length a peculiar process in which evidently dead nerve fibers retain their morphologic characteristics and are brilliantly impregnated by reduced silver (preservation necrosis). He attributed this preservation of nerve fibers to the presence of some product in the blood plasma, for it was found invariably in regions where hemorrhagic extravasation had taken place. We have found this type of necrosis in injuries to the human brain, although not as typically as Cajal described.

6. Personal communication to the authors.

This is undoubtedly due to the fact that the nerve fibers in the regions of hemorrhagic extravasations had suffered considerable injury and had undergone fragmentary degeneration, a different situation from that in the clearcut wounds of Cajal. However, in the regions of local injuries associated with hemorrhage, we found invariably a dark zone of varying width in the reduced silver preparations. On closer scrutiny we observed that this dark zone was due to an intense impregnation of granules, fragments or segments of nerve cells and fibers. The process, no doubt, is a combination of ordinary fragmentation and preservation necrosis.

SUMMARY AND CONCLUSIONS

A brief résumé is made of changes in the nerve fibers observed in Cajal's experimental work. To a great extent these observations have been confirmed by us in the study of injury to the human brain.

This contribution is based on the study of changes in the nerve fibers resulting from the common and characteristic lesions consequent to injury to the brain. Particular attention has been paid to the changes in the axis-cylinders as demonstrated by specific impregnation methods.

Interruption of nerve fibers with consequent impairment of nervous function is a common result of the various lesions of the brain consequent to injury to the head.

This interruption resulted in the formation of end-bulbs on both the proximal and the distal segment, regardless of the point of interruption. Although short-lived, those found on the proximal end of the distal segment were inclined to have a more complex structure. Those on the distal end of the proximal segment, more intensely impregnated with silver and simpler in structure, are capable of maintaining their identity for months or years.

These end-bulbs appear on fine fibrils within two hours and shortly thereafter on the medium-sized and large fibers. They are at the height of their development in four days. Those on the proximal end of the distal segment begin to be detached within two days and ultimately disappear.

The distal segment undergoes granular, fragmentary or vacuolar degeneration, ultimately leading to disappearance of the axis-cylinder. The myelin sheath also undergoes degeneration.

A peculiar combination of fragmentary and preservation necrosis was observed in local injuries associated with hemorrhagic extravasations.

PHOTOGRAPHIC STUDY OF OCULAR MOVEMENTS IN MENTAL DISEASE

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In 1908, Diefendorf and Dodge [1] reported "An Experimental Study of the Ocular Reactions of the Insane." Using the corneal reflection method, with the Dodge photochronograph, they recorded the velocity of ocular movements, the reaction time to new peripheral stimuli and the ocular pursuit reactions. They found that the speed of ocular movements does not correspond with the degree of depression or of manic excitement in the manic-depressive cases. However, in extreme cases of manic excitement the speed was greater than normal, and in markedly depressed cases it was less than normal. Cases of dementia praecox and of dementia paralytica showed abnormally rapid ocular movements; cases of chronic epilepsy, notably slow ones. In the manic-depressive psychoses the same tendency held true for the ocular reaction time to new peripheral stimuli as was noted in measurements of the speed of ocular movements. In testing pendular pursuit reactions they observed a typical broken or steplike pursuit in the cases of dementia praecox. "This peculiarity of the praecox patients has a practical as well as a theoretical interest. Practically, it is an important differentiating symptom between moderate maniacal excitement and developing praecox, i. e., between two psychoses whose differential diagnosis is of utmost importance and often of utmost difficulty."

The object of the present investigation was to explore further possible correlations between the ocular response and the underlying mental disease process. Four different optical situations were studied: (1) pursuit of a pendulum, (2) optokinetic nystagmus, (3) response to commands to look to the right and left and (4) response to peripheral

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Read by title at the fifty-ninth annual meeting of the American Neurological Association, Washington, D. C., May 9, 1933.

1. Dodge, R.: An Experimental Study of the Ocular Reactions of the Insane from Photographic Records, Brain **31**:451, 1908.

retinal stimulation. Primarily, the total response of the patient was studied. Statistical interpretation of reaction times or velocities at the upper or lower limits of adequate reactions was not attempted.

METHOD OF STUDY

Some form of graphic recording device is essential for the analytic and comparative study of the finer details of all types of ocular movements. In this work the Dodge mirror recorder has been used. This technic employs the principle of photographing horizontal conjugate deviations of a closed eye. A concave mirror pressed against the closed lid of one eye, tangential to the underlying corneal surface, reflects a recording beam of light to moving photographic paper. For a further description of the apparatus and technic the reader is referred to studies on optic nystagmus.[2]

The object of protracted visual pursuit was a pinpoint of light oscillating in the horizontal plane through approximately 30 degrees A small flashlight bulb was mounted on a black velvet screen 45 cm. from the eye. The whole screen was oscillated in harmonic motion at the end of a long, inverted pendulum. In the central position and at each end of the oscillation a wire passed through mercury cups, giving contact for a small lamp. This produced horizontal black bands on the record (fig. 1 *A*).

The stimuli for optic nystagmus were strong and compelling. White crosses on black bars were mounted vertically on the concave surface of a rotating wire mesh screen, 45 cm. from the eye. Six were placed at intervals of 40 degrees, and six at 20 degrees. A flashlight signal operated by a commutator indicated by horizontal black bands on the record each 40 degrees of rotation of the screen (fig. 1 *B* and *C*).

The stimuli for testing the saccadic or fixation movements were two pinpoints of light behind a black velvet screen placed 20 degrees apart horizontally. During command both lights were left on. Contact was made and broken in a signal circuit by the observer's synchronizing as nearly as possible with the spoken order (fig. 1 *D*). For peripheral retinal stimulation a switching device designed by Wegman [3] was used. An eccentric wheel depressed two contacts into mercury cups so that the instant one light went on the other went off. The signal light was in the same circuit as the stimulus light on the left, and therefore the exact incidence of the stimuli was registered. The switching wheel was operated by a motor so that the lights could be controlled to flash regularly or irregularly (fig. 1 *E*).

At the time of obtaining the photographic records a clinical study of the visual and ocular functions was made in each case. This included visual acuity,

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2. (*a*) Dodge, R., and Fox, J. C., Jr.: Optic Nystagmus: I. Technical Introduction with Observations in a Case with Central Scotoma in the Right Eye and External Rectus Palsy in the Left Eye, Arch. Neurol. & Psychiat. **20**:812 (Oct.) 1928. (*b*) Fox, J. C., Jr., and Dodge, R.: Optic Nystagmus: II. Variations in Nystagmographic Records of Eye Movements, ibid. **22**:55 (July) 1929. (*c*) Dodge, R.; Travis, R. C., and Fox, J. C., Jr.: Optic Nystagmus: III. Characteristics of the Slow Phase, ibid. **24**:21 (July) 1930. (*d*) Fox, J. C., Jr., Couch, F. H., and Dodge, R.: Optic Nystagmus: IV. Psychologic Conditions, ibid. **26**:23 (July) 1931.

3. Wegman: Data to be published.

visual fields on rough testing, results of ophthalmoscopic examination, pupillary reactions, tremor of the lids on active and passive closure, conjugate ocular movements on command and pursuit of the moving finger, visual attention and optic nystagmus in response to a rotating drum. The examination was necessarily incomplete in certain of the deteriorated or negativistic patients. No patient was included whose visual acuity was known to be less than 20/70 or in whom ocular palsy was present. In only one case was a gross defect of the visual field found (case 16 H; hysterical tubular vision).

The same instructions were given to each patient. He was told that a photograph was to be taken of his eyes and was shown how to sit before the camera. For pendular pursuit the instructions were: "Look at the light as it moves; follow it with your eye." For optic nystagmus the command was: "Watch the crosses." Before the fixation movements were recorded, the subject was asked to look at the light on the left and report whether or not he could see the other light. This was done to insure that the light on the right would not fall within the blind spot. He was then instructed to look at the light on the right at the command "right" and at the one on the left at the command "left." During the taking of the records only the two words "right" and "left" were used. For peripheral retinal stimulation, the instructions were: "Look at whichever light is lighted; as one goes out the other goes on."

During pendular pursuit the average length of a single record was 50 seconds. The speed varied from 2.5 to 5 seconds for one complete oscillation, the average being about 3.5 seconds. The records of optic nystagmus were somewhat longer, averaging around 90 seconds. In each case the direction of the stimuli was from right to left at the start and was reversed at the middle of the record. The velocity varied from 20 to 90 degrees per second, the average being 35 degrees (optimum). For command the average length of the record was 40 seconds, providing about fifteen auditory stimuli irregularly timed. After an initial period of about 30 seconds of retinal stimulation alternating regularly every 2 seconds, the stimuli became irregular for 60 seconds.

CLINICAL MATERIAL

Photographic records satisfactory from a technical standpoint were obtained in a total of 117 cases. The patients were obtained from three sources: 24 from the general wards of the New Haven Hospital (designated "H"); 38 from the Institute of Human Relations (designated "R"), and 55 from the Connecticut State Hospital in Middletown (designated "S"). They may be grouped as follows with respect to the conditions presented: psychoneurosis, 28; psychopathic personality, 8; dementia praecox, 43; manic-depressive psychosis, 14; dementia paralytica, 12; mental deficiency, 5; miscellaneous conditions, 7.

Every attempt to classify mental disorders is fraught with numerous hazards and satisfies the etiologic conceptions of few workers in the field. The terminology used in this report is in general agreement with that recently compiled by the National Conference on Nomenclature of Disease.

The psychoneuroses comprised chiefly anxiety states. Compulsive, obsessive, hypochondriac and neurasthenic types were also included, as well as hysteria both with and without conversion symptoms. Most of the patients in the group with psychopathic personalities were delinquents. Six of the patients with dementia praecox were in a stuporous state at the time the records were taken; 12 others had one or more times been in catatonic stupor. In addition, in 8 the condition was classified as hebephrenic and in 8 as paranoid, and in 9 it was unclassified.

The manic-depressive group included 9 depressed patients (among whom were 2 whose conditions were diagnosed as involutional melancholia), 2 with manic and 2 with mixed forms and 1 who was stuporous. The patients with dementia paralytica presented various degrees of deterioration or excitement. A psychosis was associated with 4 of the 5 cases of mental deficiency. The miscellaneous group included cases of various psychoses associated with alcoholism, epilepsy and the senile state.

EXPERIMENTAL OBSERVATIONS

The photographic data have been analyzed with respect to two of the five fundamental types of ocular movements originally described by Dodge.[4] The first of these, in which the eye follows a moving object, has been called a pursuit movement. This type occurs during pursuit of a swinging pendulum and also constitutes the slow phase of optic nystagmus. The second, the so-called saccadic type, or refixation movement, occurs whenever the point of regard wanders over a fixed section of the field of vision. Such are the responses to command and to peripheral retinal stimuli. The quick phase of optic nystagmus is also a saccadic movement.

Obviously, the photographic record obtained by a mirror recorder technic does not express itself solely in terms of these two fundamental types of ocular movements. All movements of the underlying lid of the recording eye or of the head, however slight, will be registered on the record. Such adventitious movements are readily identified; for example, the pulse wave (fig. 1 *E*), repeated winking (fig. 10 *B*), movement of the head (fig. 13 *A*) and irregular tremor (fig. 13 *D*). For discussion of these and other minor displacements of the record line the reader is referred to a previous study on optic nystagmus.[2b]

NORMAL OCULAR RESPONSE

Sections from normal records obtained from 2 patients under the four experimental conditions are shown in figure 1. It is observed that in normal pursuit (*A*) there are numerous fine rapid refixations or quick corrective movements. These appear in the records of pendular pursuits as breaks in the otherwise smooth curves. Questions of latency, the upper and lower limits of adequacy of response and the influence of psychologic factors have been subjected to previous investigation.[5]

Optic nystagmus affords an opportunity to study both types of ocular movements, pursuit and saccadic (*B* and *C*), occurring alternately in the same record. A series of moving visual objects constitutes an

4. Dodge, R.: Five Types of Eye Movements in the Horizontal Meridian Plane of the Field of Regard, Am. J. Physiol. **8**:307, 1903.

5. Dodge, Travis and Fox (footnote 2*c*). Fox, Couch and Dodge (footnote 2*d*).

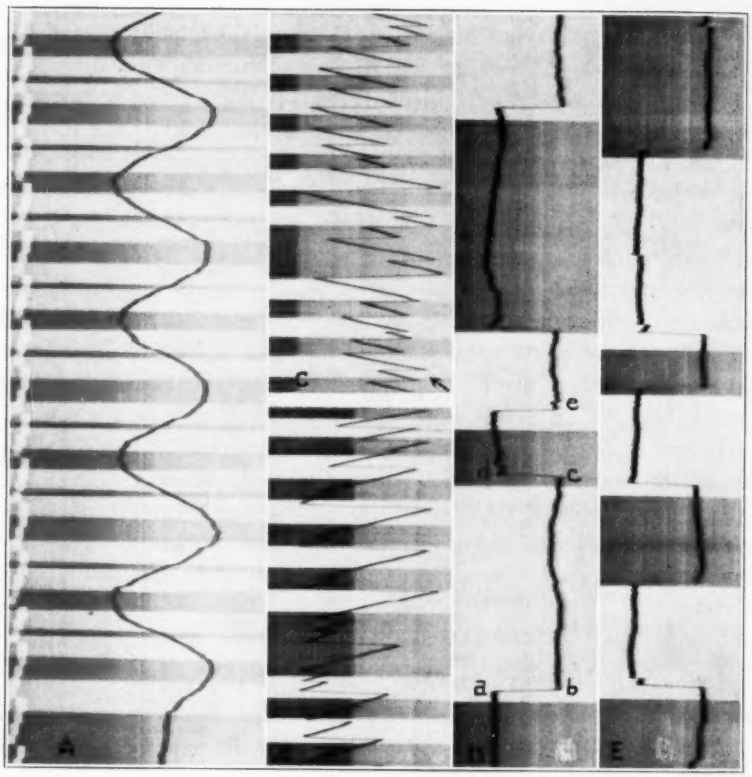

Figure 1

Explanation of Figure 1

Fig. 1 (normal response).—Figures 1 to 14 reproduce sections of photographic records obtained in each instance with the left eye recording while the right eye was seeing. The records read from below upward. The actual direction of ocular movement is reversed; i. e., movement of the line of regard to the subject's right appears as an excursion of the record line to the left. The speed of ocular movement is shown by the obliquity of the excursion. Perfectly still fixation is shown as a vertical line. The time in seconds is often recorded at the left of the record. At the bottom of each record of optic nystagmus, an arrow indicates the direction of the pursuit phase.

A. Pendular pursuit (case 1 H; anxiety state). The stimulus was a pinpoint of light on a nonconfigurated black field, moving in harmonic oscillation in the horizontal plane. The amplitude of swing corresponded to 30 visual degrees. The duration of a single complete oscillation was 3 seconds. The horizontal dark bands were made by a commutator, the broad bands representing the limit of range of the pendular oscillation and the narrow bands marking the central point of the swing.

B and *C.* Optic nystagmus (case 56 S; dementia praecox, paranoid type). The stimuli were white crosses on black bars, vertically mounted on a revolving screen. Six bars were placed at intervals of 40 degrees and six at 20 degrees. Dark bands extending across the record occur at each 40 degrees of rotation of the screen. *B* shows the response when a succession of objects was moving from right to left; *C*, when they were moving from left to right. In each instance the angular velocity of the moving visual field was approximately 35 degrees per second. The nystagmographic pattern shows the pursuit of a single object by a slow phase, suddenly interrupted by the refixation of a new oncoming object of pursuit.

D. Response on command (case 56 S). The visual stimuli were two pinpoints of light placed horizontally 20 degrees apart on a nonconfigurated black field. Commands to look to the right and to the left were given. In registering the response to command, contact was made and broken by the observer, synchronizing as nearly as possible with the spoken order. The dark bands begin with the spoken order "right" and end with the order "left." At *a*, after a latency of 0.2 second, the movement *a* to *b* begins in response to the command to look to the left. The portion of the record line *b* to *c* represents the fixation on the stimulus in the left of the visual field; *c-d* represents the response to the order to look to the right. Minor corrective refixations before arriving at the visual goal, such as that shown at *e*, occur not infrequently in normal subjects.

E. Peripheral retinal stimulation (case 56 S). The stimuli were pinpoints of light, flashing alternately, 20 degrees apart. The dark bands represent the exact period during which the light in the left of the visual field was shining. The light bands, on the other hand, represent the exact period during which the light in the right of the field was shining. The stimuli alternated in irregular fashion. Latency of response and refixation before arriving at the visual goal can be observed.

impelling type of stimulus. Studies of the character of the slow phase and investigation of the influence of angular velocity and psychologic conditions on the nystagmographic pattern have been previously reported.[2c] Disorders of optic nystagmus due to cerebral tumors and other forms of organic disease of the nervous system have been described.[6] The saccadic movements can be isolated and compared in the response to command (*D*) and to peripheral retinal stimulation (*E*). The velocity of these movements is constant. With the technic employed in the command records latency could be estimated but not accurately measured. The latency of fixation movements evoked by a different type of peripheral stimuli from those employed in this work has been previously studied.[7]

Sixteen patients showed a normal ocular response in every respect. Nine of these had psychoneuroses, while 3 showed relatively mild depression and were without retardation at the time of the experiment. Of 3 cases of dementia praecox of long standing, 1 was of the hebephrenic type, with only slight deterioration, and 2 were of the paranoid type, showing delusions but no deterioration. In addition, there was 1 case of psychopathic personality. No very sick patient showed a consistently normal response.

DISTURBANCES OF OCULAR RESPONSE DUE TO INATTENTION

The capacity for normal response was demonstrated in 60 other patients. However, the records obtained from these patients showed evidence of various disorders of attention. Examples of these disorders are illustrated in figures 2 to 6. Lapses of attention are extremely rare in the records of ocular movements obtained from normal subjects, as shown in an extensive control series.

Evidences of inattention cover a wide range. In pendular pursuit they vary from minor deviations ahead of the stimulus or cessation of response to temporary breakdown with wandering fixation. In optic nystgamus the pursuit phase may show slow drifts; the eye may momentarily remain in still fixation, or the white crosses may be ignored in favor of the mesh, during shorter or longer periods. In response to command and to peripheral retinal stimulation, in addition to showing prolonged latency and an increase in the number of anticipatory searching movements the eye may remain still or move back and forth without

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6. Fox, J. C., Jr., and Holmes, G.: Optic Nystagmus and Its Value in the Localization of Cerebral Lesions, Brain **39**:333, 1926.

7. Dodge, R., and Benedict: Psychological Effects of Alcohol, Washington, D. C., Carnegie Institution, 1915, publ. 232, p. 75.

relation to the stimulus. In figure 2, the ocular adaptation to each optical situation is interrupted by fixation on the edge of the field of view.

This group of 60 patients showing disorders of attention contained patients from all diagnostic groups. Needless to say, the attention of the subject depends in large part on his comprehension of instructions and on his desire and ability to cooperate. However, other factors play a rôle in creating a disturbance of ocular response due to inattention. For example, the 10 psychoneurotic patients did not appear less alert or more distracted than the 9 normal patients. Twenty-one of the patients with dementia praecox showed disturbances of attention alone.

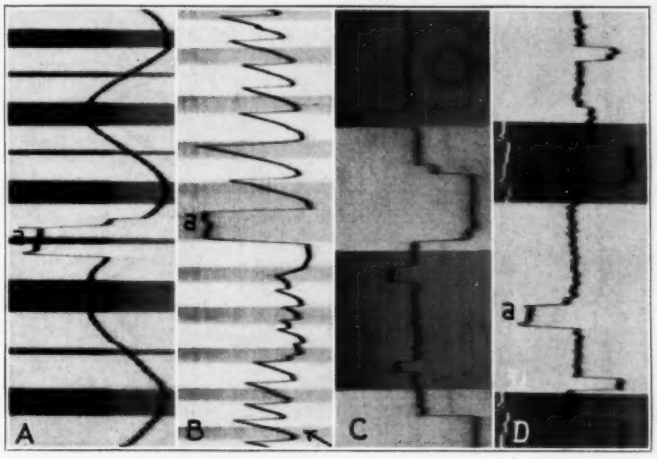

Fig. 2 (lapses of attention).—The ocular responses in each of the four experimental conditions are disturbed by a momentary lapse of attention. In each instance, the eye suddenly fixates on the edge of the field of view. After a brief period, refixation is accomplished to the preelaborated position of the stimulus. These deviations are shown at *a* in each record. *A*, *C* and *D* are records from case 78 S (dementia praecox, unclassified); *B* is from case 117 S (epilepsy with psychosis).

This applied to the chronic cases of various types. None of the 6 patients in catatonic stupor fell into this group because they showed other gross defects as well as inattention. Half of the 12 patients with dementia paralytica showed a disturbance only in optic nystagmus. All the patients with miscellaneous psychoses were inattentive in one way or another.

Correlation on the basis of the psychotic state at the time of the experiment is impossible. A few of the patients were having hallucinations during the taking of the records and reported visual and auditory

hallucinations at the conclusion of the experiment. Sudden hallucinatory experiences in themselves did not cause any deviation in the record line. In figure 3 *C* and *D*, successive records obtained one minute apart from a manic-depressive patient in stupor revealed a striking contrast in attention. A few of the patients with marked deterioration had normal ocular movements except for disturbances of attention.

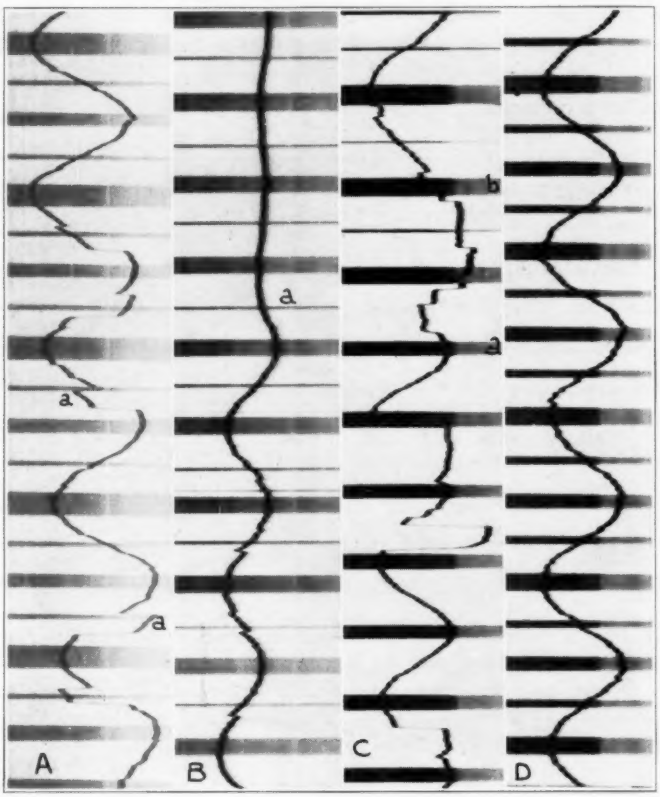

Fig. 3 (disorders of attention in pendular pursuit).—In *A* (case 20 H; hysteria) deviations of the record line occur with adequate correction. During these intervals, as at *a*, the eye is ahead of the stimulus. In *B* (case 61 S; dementia praecox, paranoid type) pursuit ceases after the point marked *a*. In *C* (case 91 S; manic-depressive psychosis, stuporous type) pursuit is interrupted by wandering fixations during one complete cycle, *a* to *b*. *D*, a record obtained one minute later, shows no evidence of inattention.

STEPLIKE INTERRUPTION OF PENDULAR PURSUIT

A minor type of defect in the ocular response to the moving pendulum is shown in figure 7. A steplike interruption of the pursuit in *B*, *C* and *D* probably represents an accentuation of the pursuit pattern shown

in *A*. In the latter, slow drifts rather than still fixations are interrupted by refixation movements. This process is merely a prolongation of the beginning phase of normal pursuit.

Steplike interruption of pendular pursuit appears in the records of 27 patients, including 14 of the 43 with dementia praecox. "Stepping" was thought by Diefendorf and Dodge to be typical of this disease. This has not proved true in our series. Although every one of the 6 patients in catatonic stupor showed varying degrees of this disturbance

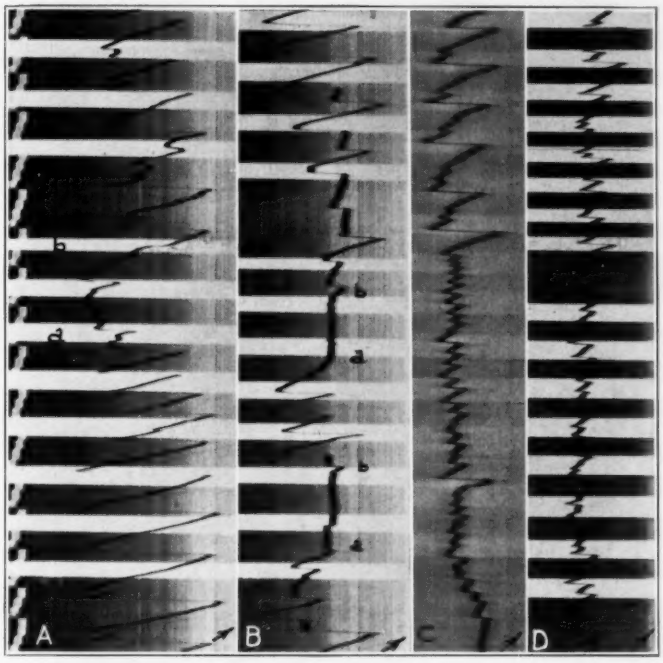

Fig. 4 (disorders of attention in optic nystagmus).—The nystagmographic pattern may be altered in varying ways and degrees. In *A* (case 111 R; mental deficiency with psychosis), for a brief interval, *a* to *b*, there are a sudden shortening and slowing of the pursuit phase. In *B* (case 115 R; epilepsy without psychosis), periods of relatively still fixation, such as *a* to *b*, alternate with normal response. In the first part of *C* (case 60 S; dementia praecox, paranoid type) and throughout the entire record *D* (case 101 S; dementia paralytica), the nystagmus is markedly shortened. (This is due to pursuit of the mesh of the background while ignoring the white crosses.)

in the records of pendular pursuit, many other patients revealed the same defect. One of these patients, whose record is shown in figure 7 *C*, a psychoneurotic man, showed a normal pursuit pattern two months later. Subsequent to the taking of these records he showed a schizo-

phrenic tendency. A similar return of the ocular response to normal was noted in case 22 H eight days after the record shown in figure 7 *D* was obtained.

Evidence obtained from our photographic data does not support the contention that stepping constitutes an early diagnostic criterion of dementia praecox. There is also no clearcut correlation with the psychotic state at the time of obtaining the records. For example, 2 patients with

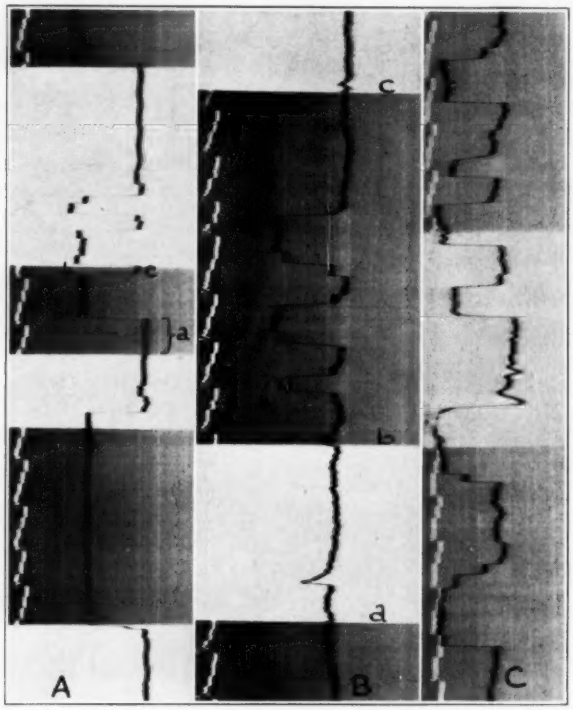

Fig. 5 (disorders of attention in response to command).—In *A* (case 72 S; dementia praecox, unclassified), a prolonged latency is shown at *a* (0.8 second). An anticipating movement, *b-c*, is followed by a series of fixation movements on the two stimuli. In *B* (case 46 S; dementia praecox, catatonic type), the commands given at the points marked *a*, *b* and *c* elicited no significant response. In contrast, the record in *C* (case 117 S; epilepsy with psychosis) shows that the patient looked back and forth at the two lights without relation to command.

depressive, 1 with manic and 1 with alcoholic psychosis showed this phenomenon in varying degrees. It is of interest that in only a single case has consistent steplike interruption of the pursuit phase of optic nystagmus been observed. This seems to answer the objection

which might be raised that stepping represents merely a form of ocular tremor. In addition, periods of still fixation in other sections of the records revealed no similar oscillation of the record line.

GROSS DEFECTS IN OCULAR RESPONSE

Gross defects were found in the records of 18 patients. They involve the response to one or more of the optical situations and point to the presence of a profound incapacity for ocular adjustment, well beyond the domain of inattention. The records illustrating the more important

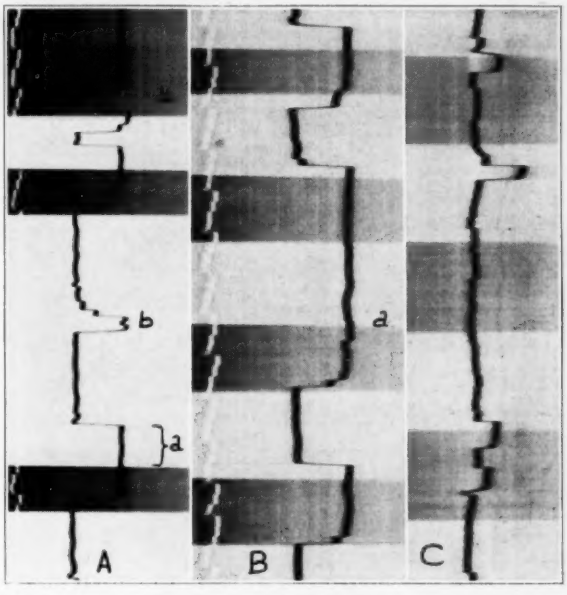

Fig. 6 (disorders of attention in peripheral retinal stimulation).—In *A* (case 72 S; dementia praecox, unclassified), latency of response is marked, especially at *a* (1 second). An anticipatory searching movement is shown at *b*. In *B* (case 116 S; epilespy with psychosis), the eye remained in still fixation instead of responding to the stimulus at the point marked *a*. Complete failure of attention is shown in *C* (case 62 S; dementia praecox, paranoid type), in which there is no relation between the irregular, wandering ocular movements and the regular alternating stimuli.

of these defects are shown in figures 8 to 10. Both types of ocular movements (pursuit and saccadic) are defective, regardless of the character of the stimulus.

In general the 18 patients in this group were the sickest ones in the entire series. Five were in catatonic stupor; 2 had chronic catatonia, and 1, an unclassified type of dementia praecox. One manic and 1

hysterical patient (tubular vision), 2 who were mentally deficient and 6 with dementia paralytica were included. The patients with dementia paralytica showed defects only in respect to optic nystagmus.

Brief summaries of a few cases, with descriptions of the records, follow.

CASE 88 S.—A housewife, aged 22, had become acutely ill two months prior to the experiment. Following a period of depression for one week she became excited, euphoric and overactive, with delusions and hallucinations. At the time of the experiment she had become more hyperactive and displayed marked distractibility

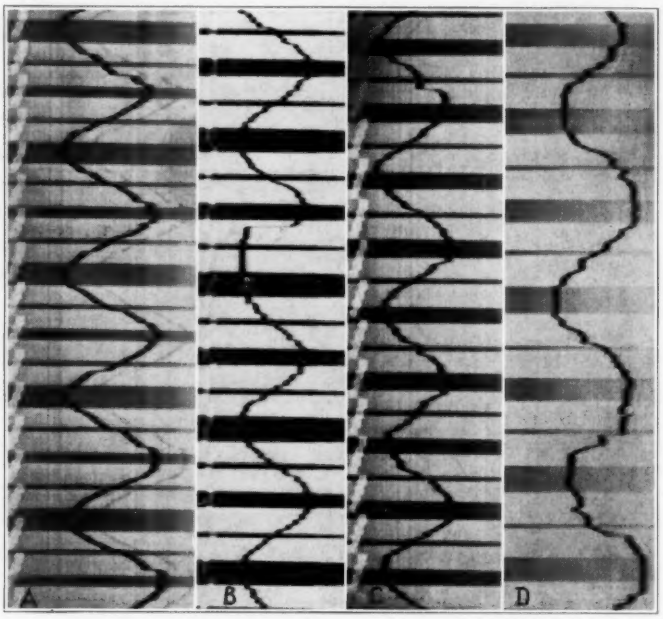

Fig. 7 (steplike interruption of pendular pursuit).—In *A* (case 10 H; anxiety state), the corrective saccadic movements observed in the normal pursuit pattern show a striking increase in length. In *B* (case 58 S; dementia praecox, paranoid type), *C* (case 26 R; hypochondriasis) and *D* (case 22 H; hysteria), steplike interruption of the pursuit phase in both directions occurs consistently throughout the records. This varies from a rhythmic, fine stepping in *B* to a gross, irregular interruption of the record line in *D*.

and flight of ideas. She continually shouted, laughed, sang and swore, but was no longer hallucinated. It was difficult to keep her before the camera.

The records of pendular pursuit show rapid shifting fixations over the entire field of view (fig. 8 *A*). However, shortly before, at the beginning of pursuit, there had been a normal response for five complete oscillations. The nystagmographic pattern was defective, with many wandering fixation movements. Response on command and on peripheral retinal stimulation was entirely absent.

CASE 52 R.—A newsboy, aged 18, had a period of marked excitement two years prior to the experiment. After eighteen months, during which he seemed to have recovered, he gradually became inactive and mute. He began to show flexibilitas cerea alternating with periods of excitement. At the time of the experiment he was mute, retarded, resistive, negativistic and considerably deteriorated. He was receiving sodium amytal.

The records of pendular pursuit show a very gross steplike response (fig. 8 *B*). The nystagmographic records showed a consistent mesh pursuit. Response on command revealed a tendency of the eye to return to its primary central position (fig. 10 *C*). The patient failed to respond to peripheral retinal stimuli.

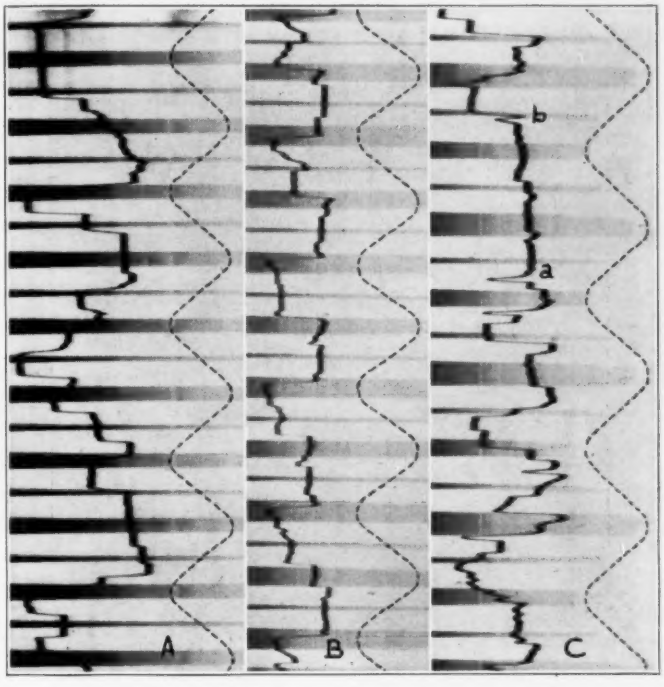

Fig. 8 (gross defects in pendular pursuit).—In none of the records is there any evidence of sustained pursuit. This is revealed by comparison with the diagrammatic representation of normal adaptive pursuit under the experimental conditions at the right of each record. In *A* (case 88 S; manic psychosis), the eye moved rapidly to all parts of the field without regard for the stimulus. In *B* (case 52 R; catatonic stupor), the eye tended to fixate alternately at the limit of swing on the pendulum, thus anticipating and waiting for the stimulus. In *C* (case 114 S; mental deficiency with psychosis), an even more bizarre response occurred, which was punctuated by a long period of relative still fixation *a* to *b*.

CASE 114 S.—A laborer, aged 32, was markedly retarded in mental development, having failed to complete the first grade in school. He had not been able to keep any employment. Following a period of agitation with hallucinations he was admitted to the Connecticut State Hospital one year previous to the experiment.

His intelligence quotient was 22. At the time of the experiment he was dull, silly and uncooperative. He continually laughed to himself and failed to respond to questions.

The records of pendular pursuit show periods of wandering movements interspersed with periods of relatively still fixation (fig. 8 *C*). The nystagmographic pattern revealed still fixations and drifts. Tests for the fixation movements evoked no response.

Case 106 S.—A laborer, aged 38, one year before the experiment gradually became irritable and restless and showed memory defects. Five months before the experiment he became assaultive and was admitted to the Connecticut State Hospital. He was euphoric and boisterous and had delusions of grandeur. The pupils were fixed to light; speech was slurred, and the spinal fluid gave positive

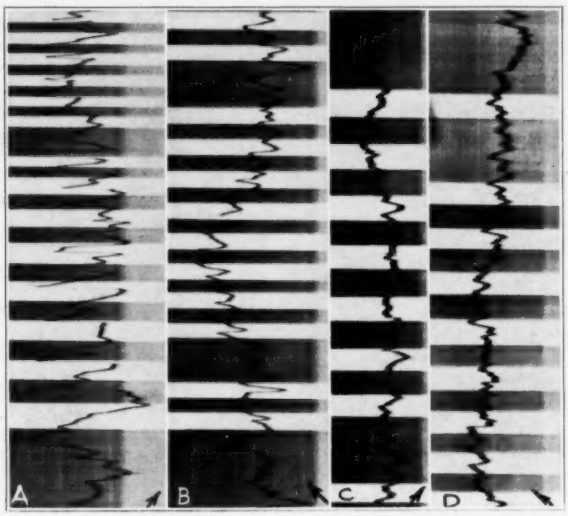

Fig. 9 (gross defects in optic nystagmus).—In none of the records, regardless of the direction, is there any evidence of sustained optic nystagmus. In *A* and *B* (case 106 S; dementia paralytica), there are shortening, irregularity and elision of the pursuit phases. In *C* and *D* (case 47 S; dementia praecox, catatonic type), there is a complete breakdown of response, revealing almost no evidence in the record of the direction of the stimuli.

serologic tests. Malaria treatment was instituted. At the time of obtaining the records he was somewhat improved but was still boisterous and had grandiose delusions.

The records of pendular pursuit show a normal response except for minor disturbances due to inattention. Optic nystagmus, however, was defective in both directions (fig. 9 *A* and *B*). When the saccadic movements were photographed, the ocular response bore no relation to command and was completely absent on peripheral retinal stimulation.

Case 47 S.—A housewife, aged 52, had been admitted to the Connecticut State Hospital nineteen years prior to the experiment. For one year she remained in a catatonic stupor and subsequently became mute and resistive. At the time of

the experiment she was dull, untidy, mute, resistive and somewhat fearful and assumed a fixed attitude.

The records of pendular pursuit show only minor deviations due to inattention. The records of optic nystagmus illustrate a markedly defective response (fig. 9 *C* and *D*). Response to command and to peripheral retinal stimuli revealed continual anticipation. The saccadic movements, however, were not grossly defective.

CASE 16 H.—A housewife, aged 40, gave a history of sudden coma, which lasted two days, six months prior to the experiment. The cause of the coma was not determined. On recovery she had partial amblyopia of the left eye. On

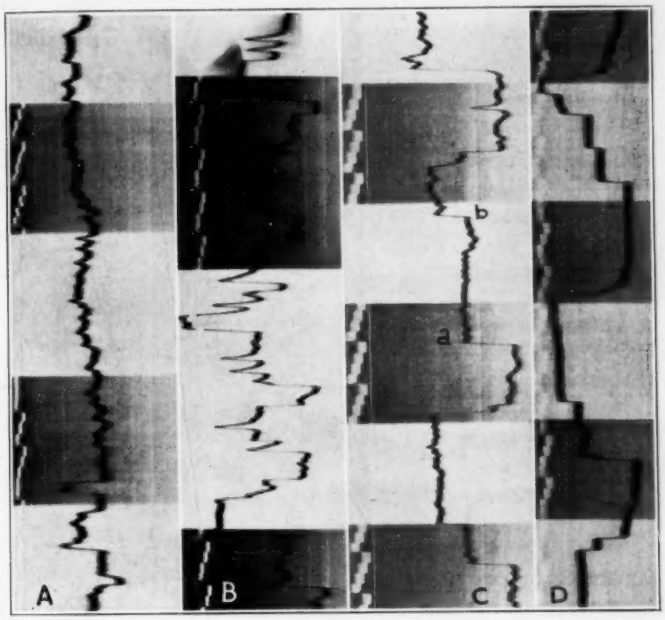

Fig. 10 (gross defects in saccadic movements).—In *A* (case 53 S; catatonic stupor), the record line is disturbed by an irregular ocular tremor but shows no evidence of response to command. In *B* (case 54 S; catatonic stupor), the ocular fixation shifts from the stimuli to the edges of the field without relation to command. In *C* (case 52 R; catatonic stupor), the response on command revealed a tendency of the eye to return to its primary central position, as at the interval *a* to *b*. *D* is the record from a case (16 H) of hysteria with tubular vision. An unusual phenomenon is observed—steplike interruption of the fixation movement.

admission to the New Haven Hospital, one week before the records were taken, she was found to have hysterical tubular vision. This was limited to 5 degrees from the fixation point as determined on the Bjerrum screen. The visual acuity was 20/70 for each eye. She also had a disinclination to move the eyes in any direction.

The records of pendular pursuit show numerous deviations from the stimulus, thought to be due to inattention. The nystagmographic pattern was normal. The

response to command and to peripheral retinal stimuli (fig. 10 *D*) revealed an unusual steplike interruption of the fixation movement. It is worthy of note that in some parts of these records the response was normal even though the stimuli fell outside of the perimetric field.

NEGATIVISM IN OCULAR RESPONSE

Three of the 6 patients in catatonic stupor showed negativism in pendular pursuit. The records of 2 of these patients are illustrated in figure 11 *A* and *B*. True negativism must be defined as more than failure to follow the pendulum. The eye must actually move in an opposite direction. There is evidence in each of these records that such a reaction took place not only in the sections reproduced but during the

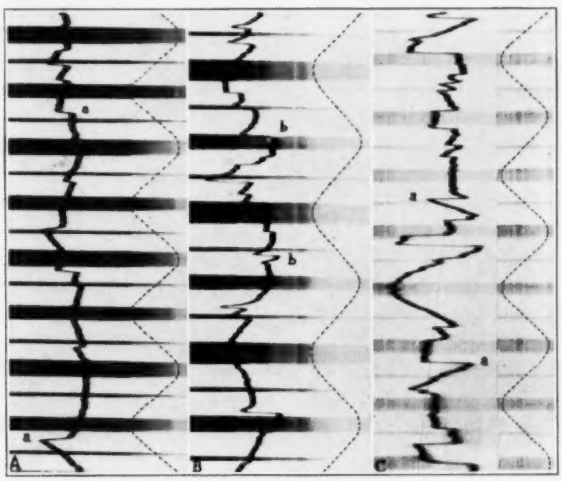

Fig. 11 (negativism in pendular pursuit).—In *A* (case 51 S; catatonic stupor), slow drifts of the eye in direction of pursuit are repeatedly interrupted by quick jerks in the opposite direction, as at *a*. During much of the time the eye remained near its primary central position in relative still fixation. In *B* (case 54 S; catatonic stupor), in addition to interruption of the normally directed pursuit phase, as in *A*, slow drifts occur in a direction opposite to that of the moving pendulum, as at *b*. *C* is the record from a normal subject attempting to avoid pursuit. Interruption of the normally directed pursuit, as at *a*, and periods of still fixation are both present. However, the slow movement is always in the direction of the stimulus and has a corresponding velocity.

major part of the experiment. This is proved by comparison with a diagrammatic representation of normal adaptive pursuit at the right of each record. In *A*, quick jerks continually interrupt the pursuit pattern and carry the eye away from the stimulus. In *B* a similar mechanism is at play and includes, in addition, slow drifts in a direction opposite to that of the pendulum. A comparison with the record (*C*) of a normal

subject attempting to avoid pursuit is instructive. Apparently a mechanism was evoked which continually interrupted the pursuit by quick fixation movements in the opposite direction but without any sign of a slow drift in the wrong direction.

The photographic evidence for negativism in optic nystagmus is suggestive but not conclusive (fig. 12 *A* and *C*). Two sections were

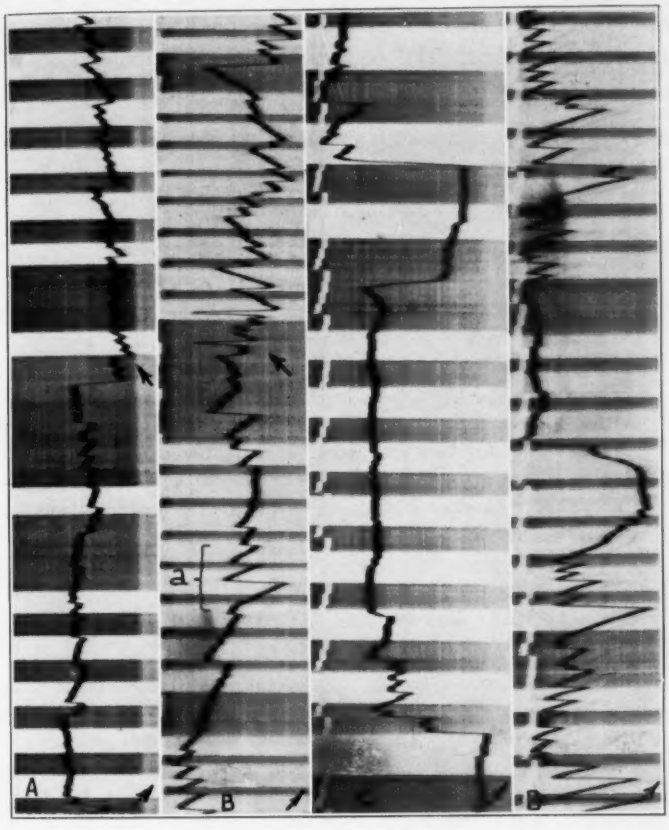

Fig. 12 (negativism in optic nystagmus).—In *A* (case 51 S; catatonic stupor), in addition to shortening of the range of the nystagmus, there is marked slowing of the pursuit phase. *B* is the record for a normal subject attempting to inhibit optic nystagmus. Similar phenomena are present except that normal nystagmus seems to break through during brief intervals, as at *a*. In *C* (case 51 S), the record shows, in large part, fixation on alternate edges of the field of view, with intermittent periods of defective nystagmus. *D* is another record from the normal subject. The temporary success in inhibiting nystagmus reveals the same mechanism as appears in *C*.

chosen from the nystagmographic records for one of the cases shown in figure 11. A comparison with the records of a normal subject attempting to inhibit optic nystagmus (fig. 12 *B* and *D*) shows the

signs of what might be considered a similar but less successful inhibitory mechanism. These consist of slowing of the pursuit phase, shortening of the range of nystagmus and fixation on the edges of the field of view.

There are uncertain evidences of negativism in the saccadic movements. Obviously absence of response must be attributed to a disorder of attention. No patient constantly looked in the wrong direction on command except the man in case 64 S, who had a delusion that his right hand was his left. The ocular response was consistent with the delusion.

Case 51 S.—A laborer, aged 19, six weeks prior to the experiment suddenly showed marked retardation, loss of interest, refusal of food, rigidity and mutism. Two weeks later he was admitted to the Connecticut State Hospital in a stuporous state. At the time of obtaining the records he was fearful, confused, mute and drooling and showed marked flexibilitas cerea. He apparently understood commands but was extremely negativistic.

The records of pendular pursuit showed negativism (fig. 11 *A*). The nystagmographic pattern also suggests negativism (fig. 12 *A* and *C*). He failed completely to respond to command or to peripheral retinal stimuli.

Case 54 S.—A machinist, aged 48, had been admitted to the Connecticut State Hospital in a stuporous state on four occasions, twenty-four, twenty, nineteen and eleven years prior to the experiment. During the periods of remission he had been able to follow his trade. The present attack began acutely four months before the taking of the records. He showed marked retardation, mutism, negativism, flexibilitas cerea and attitudinizing.

The records of pendular pursuit showed negativism (fig. 11 *B*). The nystagmographic records were suggestive of negativism. The response to command revealed gross wanderings over the field of view without relation to the auditory stimuli (fig. 10 *B*). Records of other saccadic movements were similar.

Case 53 S.—A housewife, aged 30, suddenly became disturbed and hallucinated five months prior to the experiment. Two months before the experiment she was untidy, awkward, bewildered, confused, mute and negativistic. She showed flexibilitas cerea, attitudinizing, continual moaning and blinking of the eyes. At the time of taking the photographic records she had not improved. The records were obtained with great difficulty owing to her resistance to the whole procedure.

The records of pendular pursuit showed negativism. The nystagmographic results were grossly defective, with wide excursions over the field of view. Response to command was absent (fig. 10 *A*). When she was confronted with the peripheral retinal stimuli there was hardly a trace of ocular reaction.

In none of the 3 cases just described showing evidence of negativism in certain ocular movements had the patient received sodium amytal prior to the experimental procedure. The other 3 patients in catatonic stupor were being treated with sodium amytal at the time the records were obtained.

NORMAL RESPONSES FROM VERY SICK PATIENTS

The generalization has already been made that the sicker the patient the more defective is the ocular response. However, there were numerous exceptions to this rule. For example, 3 of the patients with chronic dementia praecox revealed normal ocular responses in every respect, whereas 16 others showed disturbances of attention alone. Three of the depressed patients had normal ocular movements, and

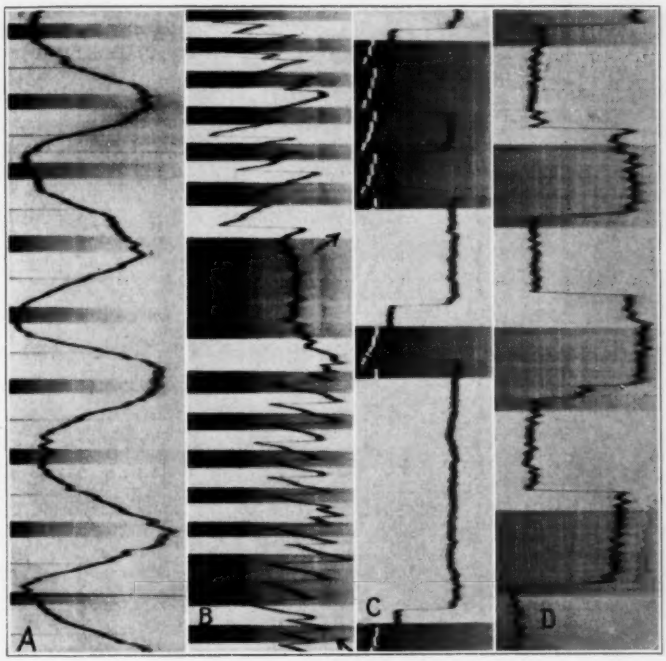

Fig. 13 (normal responses from very sick patients).—The records illustrate the capacity for a normal ocular response in each of the four experimental optical conditions. The irregularities in the record line are within normal limits of variation—in *A* caused by slight instability of the head and in *D*, by an ocular tremor. *A* is the record of pendular pursuit in case 94 S (senile psychosis with agitated depression); *B*, the record of optic nystagmus in case 45 S (dementia praecox, catatonic type); *C*, the record of response to command in case 91 S (manic-depressive psychosis, stuporous type), and *D*, the record of response to retinal stimulation in case 49 R (catatonic stupor).

several others in the manic-depressive group merely showed signs of inattention.

Figure 13 illustrates the capacity for normal adaptation to each of the optical situations by 4 very sick patients. In *A*, pendular pursuit is normal. The patient in case 94 S (senile psychosis with agitated depression) was extremely assaultive and resistive and under a terrific

tension, with delusions and hallucinations. At the time he was being fed by tube, and during the actual taking of the records he was in restraint. In *B*, optic nystagmus is normal in both directions. The patient in case 45 S (dementia praecox, catatonic type) was also resistive and assaultive and under marked tension, reacted to hallucinations and attempted to destroy the apparatus. In *C*, response to command is normal. The patient in case 51 S (manic-depressive, stuporous state) was mute and gave no sign that he understood the instructions. For comparison with records of pendular pursuit one may note figure 3 *C* and *D*. In *D*, response to peripheral retinal stimulation is normal. The patient in case 94 R (catatonic stupor) had been in a stupor for nine months. He was mute but very tense and excitable. At the time of obtaining the records he was negativistic and considerably deteriorated. Many of the records showed marked disturbances in attention, and pendular pursuit revealed irregular stepping. This patient had been receiving sodium amytal for four months and was improving slowly.

RECOVERY OF THE OCULAR RESPONSES AFTER CATATONIC STUPOR

The ocular movements of the same patient may show varying degrees of effectiveness under similar experimental conditions when photographed on different occasions. An opportunity was provided for studying the patient in case 50 R during a catatonic stupor and following recovery.

The records in figure 14 *A*, *C* and *E* were taken during the stuporous state. The patient was mute, resistive and negativistic, with marked flexibilitas cerea. He was hallucinated, occasionally smiled to himself and appeared to be markedly deteriorated. All muscular movements were extremely slow. The records do not show negativism, but they illustrate stepping and a profound disturbance of attention. He was receiving sodium amytal at the time. The records shown in *B*, *D* and *F*, taken ten months later when the patient was paroled as cured, are essentially normal. During pendular pursuit an increase in the saccadic refixation movements is noted. At this time, the patient recalled all phases of his illness and remembered the examiner and the nature of the experiment ten months previously. These observations indicate that recovery of ocular adjustment may parallel, in certain instances at least, recovery of the general adaptation of the person to his environment.

VAGARIES OF OCULAR BEHAVIOR

The records of 11 patients showed bizarre deviations of the record line. Four of these will be referred to briefly because they represent unique ocular phenomena in our experience.

In case 59 R (dementia praecox, paranoid type) the patient showed normal pendular pursuit except for two brief intervals when the eyes

suddenly deviated back and forth without fixation on any part of the field. These movements were meaningless from an optical standpoint. In case 66 S (dementia praecox, hebephrenic type) the patient during peripheral retinal stimulation gave a response at one moment which was normal except for minor disturbances of attention. A second record showed no fixation in response to the stimuli, but instead an irregular nystagmus with the quick phase to the right. The patient may have shut his eyes, in this way evoking a vestibular nystagmus, but the explana-

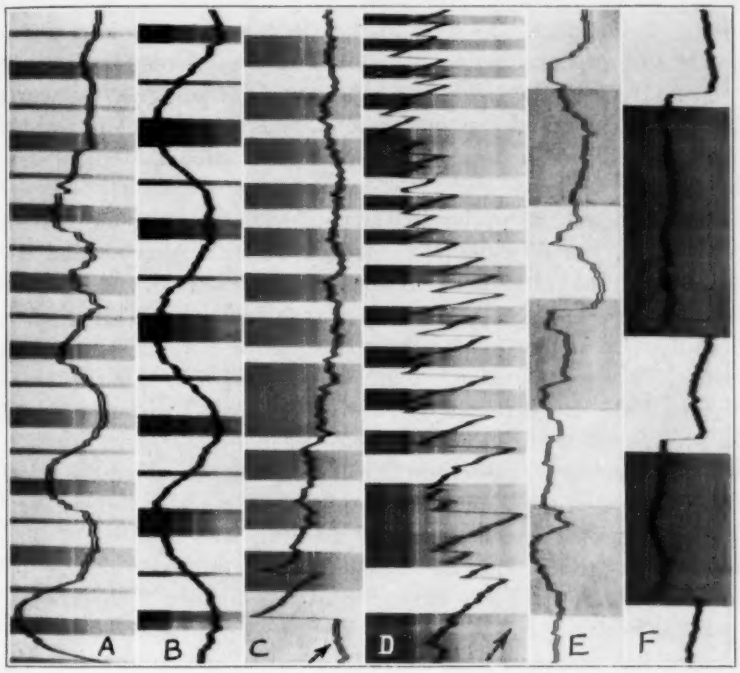

Fig. 14 (case 50 R; catatonic stupor; before and after recovery).—The ocular response obtained during the stupor and after recovery reveals, in each instance, a striking contrast. In *A*, a steplike interruption of pursuit is followed by a gradual abandonment of response. In *B*, the pursuit has become normal. In *C*, after two nystagmoid movements the response breaks down. In *D*, a normal optic nystagmus is sustained throughout the record. In *E*, irregular shifting of fixation bears no relation to command. In *F*, the saccadic movements show an effective response to command.

tion is uncertain. In case 112 S (mental deficiency with psychosis) during pursuit gross stepping suddenly developed, as if momentarily the entire learning process and preelaboration had been upset and a new order of integration begun. In case 44 S (dementia praecox, catatonic type) the movements were normal except on command, when the

saccadic movements in each direction were broken in a fine steplike pattern. The fixation movements in response to retinal stimulation were entirely normal.

SUMMARY AND CONCLUSIONS

Photographic recording of the ocular movements affords an objective approach to the study of patients suffering from mental disease. In this work we used the Dodge mirror recorder, which photographs horizontal deviations of the eyes. Four optical situations were explored: (1) pursuit of a moving pendulum; (2) optokinetic nystagmus; (3) response to commands to look to the right and to the left, and (4) response to peripheral retinal stimuli. The clinical material was composed of 117 cases, the conditions represented including psychoneuroses, different types of dementia praecox, manic-depressive psychoses, dementia paralytica, mental deficiency and a miscellaneous group of psychoses.

In 16 patients the ocular movements were found to be normal in every respect. In 60 patients the ocular response was normal except for disorders of attention. Evidence of defect or of inadequate adjustment appeared in the records of the remaining 41 patients. In over half of these a steplike interruption of the pursuit movement was present. This phenomenon, originally described by Diefendorf and Dodge in 1908 and believed by them to be characteristic of dementia praecox, was not confined to this disease group in our series.

Gross defects were present in 18 patients. They involved the response to one or more of the optical situations. They point to the presence of a profound incapacity for ocular adjustment, well beyond the domain of inattention. Both types of movements—pursuit and saccadic—were defective, regardless of the character of the stimulus. In general the 18 patients in this group were the sickest ones in the entire series.

A striking feature of the records was the variability of response. This applied not only to patients in the same diagnostic group but to individual patients under different experimental conditions. A normal response was occasionally obtained from a very sick patient.

Negativism was clearly demonstrated in the records of 3 of the patients in catatonic stupor. While watching the swinging pendulum the eye moved in a direction opposite to that of the pendulum. This was accomplished either by a quick jerk or by a slow drift in the reverse direction. In addition, gross defects in the various movements observed during the stuporous state disappeared from records taken following recovery. Such data indicate that disorders in ocular adaptation represent, in part at least, the general behavior of the person.

TREATMENT OF DEMENTIA PARALYTICA WITH TYPHOID H ANTIGEN VACCINE

REPORT OF TWENTY-FIVE CASES IN WHICH FEVER THERAPY COMBINED WITH THE ADMINISTRATION OF TRYPARSAMIDE WAS USED

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There are two generally accepted forms of treatment for pathologic changes found in dementia paralytica, namely, the production of hyperpyrexia and chemotherapy.

In 1883, Wagner von Jauregg observed the beneficial effect of intercurrent febrile disease in certain mental diseases; thus, fever therapy was suggested. As fever-producing agents he used malaria, tuberculin, Besredka's vaccine and other methods. The year 1917, however, marks the beginning of the epoch in which fever therapy was put into practice on a large scale, von Jauregg then beginning his series of malarial treatments of dementia paralytica. His results, in general, have not been altered appreciably to the present day. Plaut and Steiner, in 1919, used recurrent fever for the treatment of dementia paralytica, but their results were much less striking than those following the use of malaria. Solomon and his associates,[1] in 1926, introduced sodoku (rat-bite fever), which has theoretical possibilities equal to those of malaria but has not been accepted widely.

Petersen,[2] in 1917, demonstrated clearly the changes in the blood serum that follow the injection of a foreign protein. Cowie and Calhoun,[3] in 1919, stated that no matter what the underlying pathologic condition, an intravenous injection of a foreign protein always brought forth a characteristic reaction as regards the hemogram. Cecil, Barr and DuBois,[4] in 1922, showed that some of the fundamental changes in

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This paper was awarded the Internes Prize for 1933 at the Philadelphia General Hospital.

1. Solomon, H. C.; Berk, A.; Theiler, M., and Clay, C. L.: Use of Sodoku in Treatment of General Paralysis, Arch. Int. Med. **38**:391 (Sept.) 1926.

2. Petersen, W. F.: Serum Changes Following Protein "Shock" Therapy, Arch. Int. Med. **20**:716 (Nov.) 1917.

3. Cowie, D. M., and Calhoun, H.: Non-Specific Therapy in Arthritis and Infections: A Study of Changes in Blood Consequent on Intravenous Injection of Typhoid Protein; a Consideration of Analogy Between Typhoid Paroxysm and Malarial Paroxysm, Arch. Int. Med. **23**:69 (Jan.) 1919.

4. Cecil, R. L.; Barr, D. P., and DuBois, E. F.: Clinical Calorimetry: Temperature Regulation After Intravenous Injection of Proteose and Typhoid Vaccine, Arch. Int. Med. **29**:608 (May) 1922.

the physiologic processes after foreign protein shock were identical with the changes observed during a malaria paroxysm. On this basis, Kunde, Hall and Gerty,[5] in 1927, instituted treatment of dementia paralytica by means of whole typhoid vaccine.

Neymann and Osborne,[6] in 1931, offered diathermy treatment in an attempt to show whether the results obtained after malaria were attributable to the reticulo-endothelial response or to fever alone. Their results were reported as good, but the controversy on this point is still unsettled. Robinson and Johnson,[7] in 1932, advocated diathermy combined with other forms of therapy.

The specific fight against the spirochete by chemicals began with the introduction of arsphenamine by Ehrlich in 1910. The use of this drug in early systemic syphilis was thought to have aborted, to a degree, involvement of the nervous system. This has since been denied by many observers. Hammond, Sharp and Smith,[8] in 1917, injected arsphenamine into the lateral ventricles of the brain in the treatment of dementia paralytica, but their results were not conclusive. Lorenz and his co-workers,[9] in 1924, demonstrated a tonic effect and serologic improvement in syphilis of the nervous system following the intravenous administration of tryparsamide. They proved that the use of this substance made possible an increase in the amount of arsenic reaching the brain substance, thus producing more rapid resolution of the inflammatory exudate and enhancing the removal of waste products from the involved areas. Tryparsamide has since become one of the most widely used chemicals for the direct treatment of neurosyphilis.

Various attempts have been made to treat patients for dementia paralytica by the intraspinal and intracisternal routes, with the thought of attacking the diseased tissues more directly. Dercum showed that this was not a rational procedure since the medication thus introduced drained off through the venous sinuses too rapidly to be effective.

Perhaps the most recent therapeutic agent introduced for the treatment of dementia paralytica is ultraviolet irradiation. Mella and

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5. Kunde, M. M.; Hall, G. W., and Gerty, F. J.: General Paralysis: Effect of Nonspecific Protein Therapy on Blood and Spinal Fluid, J. A. M. A. **89**:1304 (Oct. 15) 1927.

6. Neymann, C. A., and Osborne, S. L.: Treatment of Dementia Paralytica with Hyperpyrexia Produced by Diathermy, J. A. M. A. **96**:7 (Jan. 3) 1931.

7. Robinson, G. W., Jr., and Johnson, P. A.: Hyperpyrexia in Treatment of Dementia Paralytica, J. Missouri M. A. **29**:121, 1932.

8. Hammond, G. M.; Sharp, N., and Smith, J. W.: Treatment of Paresis by Injections of Salvarsan into the Lateral Ventricle, J. A. M. A. **69**:23 (July 7) 1917.

9. Lorenz, W. F.; Loewenhart, A. S.; Reitz, T. F., and Eck, C. P.: The Use of Tryparsamide in Neurosyphilis, Am. J. M. Sc. **168**:157, 1924.

O'Neill,[10] in 1932, gave 30 erythema doses over the entire body to unimproved Wassermann-fast patients on whom fever and chemotherapy had little effect. They reported good clinical improvement, but their work is yet to be confirmed.

A great variety of other measures have been tried in the treatment of syphilis of the nervous system, only to be discarded in favor of combined fever treatment and chemotherapy.

TREATMENT WITH TYPHOID H ANTIGEN VACCINE

Fever therapy is now a generally accepted measure in the treatment for dementia paralytica. The three popular forms, namely, malarial inoculation, the use of whole typhoid vaccine and diathermy, are now used in the psychopathic wards of the Philadelphia General Hospital. Yet there are patients who are not fit subjects for any one of these types of treatment. Patients with more advanced cases cannot withstand the rigors of malarial inoculation; moreover, the racial immunity of Negroes (20 per cent of the total group) to inoculated malaria precludes this measure to some extent. It was not considered justifiable to subject debilitated patients to the severe systemic reactions induced by whole typhoid vaccine. Many patients are so agitated that the risks of diathermy (burns and pressure sores [Prior[11]]) are not inconsiderable. My colleagues and I, therefore, endeavored to find a safe, simple and inexpensive fever-producing agent which would give a sufficiently high temperature with minimum danger and inconvenience to the patient. We have found that typhoid H antigen vaccine answers well. This is a water-clear saline filtrate containing the flagellar (H) antigen of the organism, the somatic (O) antigen having been blocked by phenol. The protein content of the H antigen solution is quantitatively equal to that of the whole suspension from which it is prepared; it differs qualitatively, however, as shown by the type of reaction following intravenous administration. The paroxysm is relatively constant in all persons.

The reaction following the intravenous injection of H antigen as compared with that seen after an injection of whole typhoid vaccine differs to an appreciable degree. With H antigen, the rise in temperature is more constant, reaches a slightly higher level and maintains its peak for a longer time; the decline in temperature is more gradual than that usually seen following injection of the whole vaccine. Its greatest advantage over the whole vaccine, however, lies in the far less severe systemic reaction; *the patients are not nearly so sick.* About one hour

10. Mella, H., and O'Neill, R. T.: Ultra-Violet Irradiation in General Paresis, M. Bull. Vet. Admin. **9**:29, 1932.

11. Prior, G. P. U.: Diathermy in Treatment of General Paralysis of Insane, M. J. Australia **1**:882, 1932.

after the injection of H antigen the patients usually (some do not) have a chill of moderate severity with a simultaneous dull ache in the lumbar spine and the calves of the legs, which subsides with the chill. During the following rise in temperature they feel comfortable and do not have the headache, orbital pain, nausea and vomiting that we have observed so frequently with whole vaccine. Our experience has led us to believe that the burden on the already diseased tissues of the patient is sufficiently light and that typhoid H antigen vaccine can be used with relative impunity in the less physically fit subjects.

The advantages of typhoid H antigen as compared with malaria are many. It is a standard product, readily available and easily administered; the paroxysms are easily controlled by graded doses. It is feasible for use with patients outside the hospital. It affords a clean injection of a sterile solution. To superimpose one disease on an already existing one often introduces untoward complications. Henry,[12] in 1932, listed twenty-one major and nine minor complications that one might encounter after malarial inoculation. A second question must be considered: Should one take the malaria organism from a patient with a four plus Wassermann reaction of the blood and spinal fluid and inject it into a patient with a negative reaction of the blood but a positive reaction of the spinal fluid and so enhance an infection of the blood? That malaria will produce marked prostration, anemia and loss of weight is well known; malarial inoculation of any patient implies the possibility of death, some fatalities being recorded. The maintenance of general good health and the absolute safety from endangering the patient's life by the use of H antigen vaccine are conspicuous when compared with the results of treatment with malaria.

Unlike diathermy, typhoid H antigen vaccine does not offer the risks of electrode burns and pressure sores that may follow the sweating and immobility of the tightly wrapped patient. Schamberg and Butterworth,[13] in 1932, reviewed twenty-six cases in which the most recently advocated technic for diathermy was employed; they reported burns in nine cases (34.5 per cent). Typhoid H antigen vaccine also has no apparent effect on the kidneys, whether healthy or diseased. Diathermy, according to our experience, can be given only to the more robust patients.

We find, therefore, that typhoid H antigen vaccine has fewer contraindications than any other agent used for inducing hyperpyrexia. Its contraindications are four: (1) severe cardiorenal disease; (2) active

12. Henry, C.: A Progress Report on Routine Practice of Malaria Therapy, M. J. Australia **1**:888, 1932.

13. Schamberg, J. F., and Butterworth, T.: Diathermy in Treatment of General Paralysis and in Wassermann-Fast Syphilis, Am. J. Syph. **16**:519, 1932.

pulmonary disease; (3) severe cachexia, and (4) acute infection with rapid sedimentation.

Typhoid H antigen vaccine produces no complications of any consequence. In one case, not recorded, herpes labialis and a corneal ulcer developed following the fever. Both subsided after local treatment. No other complications have appeared that can be directly attributed to the injection of foreign protein.

CLINICAL INVESTIGATIONS

The object in this series of cases was to produce, through the intravenous administration of typhoid H antigen vaccine, a rise in temperature to above 102 F., this temperature being considered the minimal level of adequate therapeutic hyperpyrexia; to maintain the fever as long as possible, and to administer tryparsamide simultaneously with the fever reaction. Tryparsamide is given when fever has been produced for two reasons: 1. We believe that the period of hospitalization is shortened thereby. 2. We believe, as shown by Lorenz and his co-workers,[9] that tryparsamide owes its curative properties to its ability to permeate the cerebral vessels and to its remarkable penetrative power for the nervous system. We believe that its permeation into the brain is facilitated by giving it to the patient *at the height of the fever when the vessels are dilated;* thus it is logical that an increased amount of arsenic reaches the brain to enhance the reduction of inflammatory exudate, inhibit further deterioration and promote healing of the damaged areas.

MATERIAL AND METHODS

Patients were selected in whom malaria was contraindicated and the use of whole typhoid vaccine and diathermy was deemed inadvisable because of their physical condition. The series included twenty-five patients (twenty-one men and four women); five were Negroes (four men and one woman), and twenty were white (seventeen men and three women). The age limits were 27 and 68 years, with an average of 40 years. Fifteen patients gave a history of a primary lesion from ten to twenty-three years previously, and thirteen of these had received treatment for systemic syphilis. Not one, to our knowledge, had received any specific treatment for syphilis of the central nervous system. Nineteen patients showed definite signs of dementia paralytica, with colloidal gold curves of the zone 1 type; six patients showed zone 2 type curves, with a mental aberration of the type of manic-depressive psychosis; (four of the latter patients were excited, and two, depressed); two patients showed zone 1 type curves but no mental symptoms.

As preliminary preparation, the patients were weighed; chemical examination of the blood, urinalysis, blood counts and examination of the spinal fluid were made; the necessary ophthalmoscopic examinations to determine whether tryparsamide could be used were also made.

Injections were given three times a week intravenously; a 26 gage hypodermic needle was used to prevent damage to the vein, to give the injection slowly and

Type of Case, Amount of Treatment Given and Clinical and Serologic Changes

No.	Name	Age	Sex	Race	Time Between Onset of Symptoms and Treatment	Type of Involvement of Central Nervous System	Number of Injections of		Temperature Range, F.	Average Temperature Peak, F.	Total Hours Temperature Above		Wassermann Reaction of Blood		Wassermann Reaction of Spinal Fluid		Colloidal Gold Curve		Clinical Improvement
							Antigen H	Tryparsamide			102 F.	101 F.	Before Treatment	After Treatment	Before Treatment	After Treatment	Before Treatment	After Treatment	
1	W. M.	40	M	W	1 yr.	Demented	15	0	100-105	102.2	53	78	1+	Neg.	4+	4+	3433331100	2333221000	Good
2	V. S.	55	M	W	3 yrs.	Demented	17	20	102-106	103.5	109	156	4+	4+	4+	4+	5555544310	5555532100	Good
3	W. F.	36	M	W	5 yrs.	Excited	9	0	100-104	102.2	24	63	4+	4+	4+	4+	5554442100	.....	Fair
4	M. R.	35	M	W	1 yr.	Demented	11	7	101-106	102.5	32	59	Neg.	...	4+	...	3533110000	.....	None
5	M. L.	66	F	W	4 mos.	Depressed	16	10	101-104	102.8	28	54	4+	4+	4+	4+	4555455300	1123332100	Marked
6	J. L.	59	M	B	9 mos.	Demented	16	10	100-104	102	25	42	4+	4+	4+	4+	4554332100	1123321000	Fair
7	P. G.	38	M	W	7 yrs.	Excited	18	25	100-103	101.6	32	55	4+	1+	4+	4+	3454433100	0012311000	Good
8	J. S.	30	M	W	7 mos.	Excited	15	10	100-104	102	39	59	4+	4+	4+	4+	5555555543	5555532100	Marked
9	S. F.	41	M	W	7 mos.	Depressed	15	0	101-105	103	51	75	4+	4+	4+	4+	3554443200	1123100000	Good
10	R. J.	45	M	W	4 mos.	Depressed	15	10	100-104	101.7	35	47	3+	4+	4+	1+	1111321000	0001110000	Good
11	D. T.	32	M	B	2 yrs.	Excited	18	24	101-104	102.3	24	45	Neg.	Neg.	1+	Neg.	1123320000	1233321000	None
12	W. M.	35	M	W	6 yrs.	Excited	13	0	101-104	103.2	22	36	4+	4+	4+	4+	5555554310	4555543210	None
13	W. N.	39	M	B	?	Depressed	17	25	101-104	102.4	27	58	1+	1+	4+	4+	4555553321	3455553200	Marked
14	J. R.	68	M	W	4 mos.	Excited	17	29	101-104	102.3	33	66	4+	4+	4+	4+	2233421000	1233321000	Marked
15	A. H.	35	M	W	6 yrs.	Agitated	19	16	101-105	103.4	63	83	4+	4+	4+	4+	5555555310	5555543320	Fair
16	T. T.	35	F	W	2 yrs.	Agitated	17	0	102-105	103	49	82	4+	4+	4+	4+	5555542100	5555543210	Marked
17	A. A.	57	M	W	11 yrs.	Excited	18	0	102-106	104	60	77	4+	3+	4+	4+	3344432100	1223321000	None
18	R. L.	42	F	W	1 yr.	Agitated	17	25	101-104	102.7	45	73	2+	3+	4+	4+	4444543210	4333321000	Good
19	H. F.	40	M	W	6 mos.	Depressed	25	10	100-104	102	48	114	Neg.	Neg.	4+	4+	2555432000	5555533210	Fair*
20	F. N.	51	M	W	None	No dementia paralytica	8	3	102-105	103.9	38	51	Neg.	1+	3+	2+	3444421100	3333210000	Good*
21	C. S.	27	M	B	10 mos.	Excited	18	23	102-105	103.7	79	110	4+	4+	4+	4+	4555553210	5555553210	Fair†
22	G. L.	56	M	W	None	No dementia paralytica	15	4	101-104	102.2	24	49	2+	4+	4+	4+	5554432110	5543321000	Fair
23	J. R.	56	M	W	7 mos.	Depressed	14	10	101-106	102.5	35	54	2+	±	4+	4+	5555543210	5555543210	Good
24	E. H.	30	F	B	1 yr.	Agitated	27	0	100-105	102.2	58	80	4+	Neg.	4+	4+	5533354321	5555554321	Fair
25	J. M.	50	M	W	6 mos.	Depressed	21	10	102-107	103.9	59	86	1+	Neg.	4+	4+	5555554310	5555555321	Good

* Amblyopia.
† Jaundice.

to cause the least possible discomfort to the patient. The initial dose used was 50 million organisms (killed bacilli equivalent), and the reaction obtained was a fair index for the calculation of subsequent doses. H antigen builds up a partial immunity, as does whole vaccine, so that increasing doses must be given in subsequent injections. The dose for the second injection was usually 200 million organisms, and that for the third, 400 million, the number advancing 200 million for each paroxysm to the sixth injection (1 billion organisms); after this it was found better to increase each dose by 400 million organisms. Doses as high as 8 billion organisms have been given.

Several patients gave a history of typhoid and showed no reaction after injections. To overcome this we prepared the H antigen from paratyphoid A organisms, to which they had no immunity, the dose being the same as that already outlined; following this, the reaction was good. In patients who reacted well to typhoid H antigen but during the course of the treatment developed an immunity to it, we changed to paratyphoid A antigen H and continued with succeeding doses. If an immunity to paratyphoid A antigen H developed, as shown by succeeding less satisfactory rises of temperature, equal parts of a mixture of H antigen of both typhoid and paratyphoid A were given; it was found that this could be continued indefinitely.

The paroxysms were characteristic and consistent. A moderately severe chill occurred from one to one and one-half hours after the injection and lasted for from five to forty minutes, accompanied by a few pains in the lumbar region and in the legs. Coincidentally with the chill, the temperature began to rise; it reached its peak from two and one-half to three hours after the injection. The peak usually varied between 102 and 105 F. and was maintained for one-half hour; after this the temperature gradually declined, reaching the normal level from eight to nine hours after the inoculation. The pulse rate at the height of the fever varied between 90 and 120, usually being below 110. Never did it rise above 120.

Since it is believed that the good results obtained by malaria are due partly to prolonged fever, we endeavored to prolong the rise of temperature, following somewhat the idea of Nelson. We were satisfied with the peak produced by the initial dose, so for investigative purposes we followed it by the injection at varying intervals of a dose equal to one half of the initial dose given on that day. We found that when the second dose was given three hours after the first injection, at the height of the fever, the peak was maintained for from one to two hours longer. The second injection rarely caused a slight chill.

Once a week, to patients for whom it was not contraindicated, 3 Gm. of tryparsamide was given intravenously. This was given in lieu of the second injection of H antigen, at the height of the fever, i. e., three hours after the first injection of H antigen. We found this a valuable adjunct to the treatment; it did not increase the dangers of arsenical intoxication. No systemic reactions followed its administration when given in this manner.

In the latter part of the series we wrapped the patient in rubber sheeting and woolen blankets immediately after the injection, before the chill. This raised the temperature to a higher level, from 104 to 106 F., and maintained it for from four to six hours. This procedure dispensed with the second injection of H antigen used to maintain the fever. It is somewhat analogous to treatment with diathermy but involves no risk of burns and requires no machine, and the patient does not have to be watched so closely as with diathermy.

The average series consisted of from fifteen to twenty paroxysms during six weeks. Tryparsamide was continued at weekly intervals after the fever treatment

was completed. If a second course of fever therapy was indicated, the patient was given a two week rest period, during which he lost tolerance for H antigen vaccine. The second series of injections was carried out precisely like the first, except that larger subsequent doses had to be given because tolerance developed more rapidly. At the close of each series the initial laboratory examinations were repeated, and the clinical and serologic changes were noted.

RESULTS

The difficulty encountered in using a biologic agent, such as typhoid H antigen vaccine, is that the results of no two investigators are comparable. This is due not only to the variety of patients treated but to the variation in the strains of organisms used in the preparation of the vaccine. One strain will give fairly constant results, but these cannot be expected to coincide closely with the results of another investigator using a different strain.

Considering the type of patients treated, i. e., those not physically able to withstand the usual more heroic measures, our results were good. The patients were well satisfied and did not object to the treatment.

In computing results, we employed the usual method of comparing symptomatic with serologic improvement. We noted that a single course of fever paroxysms caused no alteration in the Wassermann or the Kahn reaction of either the blood or the spinal fluid. There was a tendency, however, to lower the colloidal gold curve from a zone 1 type to a zone 2 type in some cases; this, however, can occur following any of the usual treatments for dementia paralytica (Novy,[14] 1932). The changes in the gold curve did not run parallel to the degree of clinical improvement. It was found that there was as much serologic improvement in the clinically unimproved as in the clinically improved patients. Such a finding is not conclusive, since the patients have been observed for only one year (Hubbs, 1931).

The clinical improvement in most cases was soon evident. There was a subsidence of nervousness and emotional instability. (All but four of the patients gained weight, from ½ to 18 pounds [0.2 to 8 Kg.]; these four lost from 1 to 6 pounds [0.5 to 3 Kg.]). Many showed improvement in memory and judgment. There were no changes in the pupils, tendon reflexes, etc., but there was a subsidence of tremors. Chemical examinations of the blood showed no alterations in the sugar and urea nitrogen.

We divided the patients into four groups, depending on the degree of clinical improvement, at an average of six months after treatment was begun. This grouping was selected as being more specific than

14. Novy, F. G., Jr.: The Significance of the Colloidal Gold Reaction as a Diagnostic and Prognostic Aid in Neurosyphilis, Am. J. M. Sc. **184**:401, 1932.

that under the usual term "remission." Improvement is in four degrees: (1) marked improvement, five patients (20 per cent); (2) good improvement, nine patients (36 per cent); (3) fair improvement, seven patients (28 per cent), and (4) no improvement, four patients (16 per cent). The patients were again divided into three groups as regards the adjustability to the original environment: (1) discharged and able to make adjustment at home, eleven patients (44 per cent); (2) improved and making an adjustment in an institution, ten patients (40 per cent); (3) making no adjustment, four patients (16 per cent).

Seven of the twenty-five patients received fever therapy alone, tryparsamide being contraindicated because of changes in the optic nerve. Varying degrees of clinical improvement were noted. T. T. (case 16), a woman, showed marked improvement and was discharged to her home to resume her domestic duties. Two men showed good improvement; S. F. (case 9) resumed work as a tailor, and W. M. (case 1), having no home, made a good adjustment in an institution. Two patients showed fair improvement; W. F. (case 3) was taken from the hospital prematurely against advice, so the treatment was incomplete; E. H. (case 24) was discharged to her home in good condition to resume her household duties. Two showed no improvement: A. A. (case 17) made a fairly good adjustment in an institution, but six months later rapidly became demented; W. M. (case 12) showed marked manic manifestations; he was taken from the hospital after a short course and died two months later from rapid deterioration due to dementia paralytica.

The height of the temperature attained was usually in direct proportion to the severity of the preceding chill. The patient's improvement, however, was found not to be directly proportional to the height of the temperature obtained. There was a more direct relationship between the total hours of temperature above 102 F. that a patient presented and his clinical improvement. The calculation of the total hours of fever that a patient should have depends on the type and the extent of involvement of the central nervous system. We now believe that in outlining a series of fever paroxysms more attention should be directed toward the total hours of temperature above 102 F. than to a stipulated number of paroxysms, since the latter in many cases is too variable.

The remaining eighteen patients received a varying number of injections of tryparsamide during the course of the fever therapy. General improvement in the patients receiving combined fever and tryparsamide therapy was more pronounced than in those receiving fever therapy alone. However, it was noted that the tendency to lowering of the colloidal gold curve was as pronounced in patients receiving fever therapy

alone as in those given combined treatment. Of the eighteen patients receiving combined fever and tryparsamide therapy, four showed marked improvement; seven, good improvement; five, fair improvement, and two, no improvement. Of these eighteen, seven made a good social adjustment in their previous environment, nine were improved and made a good adjustment in an institution and two made no adjustment.

In three of the twenty-five patients complications developed: In C. S. (case 21), a colored man, jaundice suddenly developed, following the tenth injection of tryparsamide; this, we believe, was due to arsenical hepatitis; the jaundice subsided after a two months' rest. F. N. (case 20), a white man, experienced a sudden complete amblyopia after the third injection of tryparsamide; all treatment was discontinued, and in two weeks vision returned but was tubular. H. F. (case 19) had a slowly progressing amblyopia following the completion of a course of ten injections of tryparsamide; the blindness became complete after three weeks and has persisted. A complete study of the case indicated that the blindness was due to syphilitic optic atrophy rather than arsenical in origin.

SUMMARY

We believe that we have developed a method for the adequate treatment of dementia paralytica, especially in patients who are physically unfit to withstand the more heroic measures. We believe typhoid H antigen vaccine to be far superior to the usually used whole typhoid vaccine as a fever-producing agent. H antigen vaccine, when properly administered, will produce a more uniform rise of temperature, the fever will persist longer and will not subside as quickly as does that following an injection of whole typhoid vaccine. Most important is the fact that the fever is produced with relative safety and lack of malaise to the patient. We have also been able to give more intensive treatment by combining the administration of tryparsamide with the fever treatment, with beneficial results. We advocate the continued use of tryparsamide indefinitely after the fever therapy has been completed.

CONCLUSIONS

1. Twenty-five patients with dementia paralytica, physically unsuitable for treatment with malaria, whole typhoid vaccine or diathermy, were treated with typhoid H antigen (flagellar) vaccine alone and in combination with tryparsamide.

2. The symptomatic and serologic improvement obtained by this method compares favorably with results obtained with other forms of fever therapy.

3. Typhoid H antigen vaccine is indicated for persons who cannot withstand the rigors of the other heroic forms of therapy because: (*a*)

although the hyperpyrexia equals that obtained with whole typhoid vaccine, the concomitant illness is far less severe; (*b*) it does not involve superimposing a second (and perhaps lethal) infection on an already existing one, as with malaria; (*c*) it does not involve the risk of burns and renal damage, as with diathermy; (*d*) its contraindications are but four, namely (1) severe cardiorenal disease, (2) active pulmonary disease, (3) severe cachexia and (4) acute infection with a rapid sedimentation rate; (*e*) its administration and control are simple, and its use in the hands of the general practitioner, both in the hospital and in the home, is safe; (*f*) it has not, in our hands, been associated with complications or sequelae.

4. More attention should be directed to the total hours of fever produced in a patient than to a definite number of paroxysms.

5. Tryparsamide can be given at the height of the fever with better clinical results and no increase in the dangers of complications.

Thirty-Fourth and Pine Streets.

SENSORY THRESHOLD TO DIRECT CURRENT STIMULATION IN SCHIZOPHRENIC AND IN NORMAL SUBJECTS

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Observations reported by Grabfield [1] on the faradic current threshold as an index of "general nervous irritability" in patients with dementia praecox indicated that high thresholds were found constantly in 33 per cent of his patients and at times in as many as 48 per cent. As a preliminary to an investigation into the theoretical and practical significance of these observations, the present study was conducted to make certain of the existence of differential thresholds.

The method employed by Grabfield was that of Martin,[2] which consists essentially of determining the threshold for make or break induction coil shocks. The second and third finger-tips of the observer's left hand were placed in liquid electrodes forming part of the secondary circuit. The experimenter, in another room, sent shocks of gradually increasing intensity (by tightening the coil coupling) until the subject pressed a key, indicating that he had experienced the shock. For each subject four such determinations were made, one with no secondary resistance, one with a resistance of 5,000 ohms in series with the secondary, one with 10,000 ohms and one with 15,000 ohms. Grabfield reported that as a check these coil positions were "tried and retried."

This procedure is faulty because there were not enough observations for accurate comparisons; an ascending series alone does not yield true thresholds; the absence of a preparatory signal may result in higher values; unpracticed subjects usually give greater variation, and the level of performance of psychotic subjects is likely to be lower when they

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This study was conducted with the cooperation of the research staff of the Worcester State Hospital.

From the Memorial Foundation for Neuro-Endocrine Research, Boston, and the Psychology Department of the Worcester State Hospital.

1. (*a*) Grabfield, G. P.: Variations in the Sensory Threshold for Faradic Stimulation in Psychopathic Subjects: First Note, Boston M. & S. J. **171**:883, 1914; (*b*) Variations in the Sensory Threshold for Faradic Stimulation in Psychopathic Subjects: III. The Dementia Praecox Group, ibid. **173**:202, 1915.

2. Martin, E. G.: The Measurement of Induction Shocks, New York, John Wiley & Sons, Inc., 1912, pp. vii and 117. Martin, E. G.; Porter, E. L., and Nice, L. G.: The Sensory Threshold for Faradic Stimulation in Man, Psychol. Rev. **20**:194, 1913.

are placed in a separate room from the experimenter. Also, varying shock intensity by changing the coupling of the induction coil varies the wave form.[3] Consequently, a technic of stimulation by direct current developed by Miles,[3a] which obviates the latter complication, was adopted.[4]

MATERIAL AND METHOD

The observers, both normal and schizophrenic, were each tested twice at intervals of three months between 8:30 and 11:30 a. m. and 1:00 and 4:00 p. m., with the exception of two normal subjects on the first test, one of whom was examined at 12:45 p. m. and one at 4:15 p. m. The observer's finger-tips were cleaned with alcohol and examined carefully for abrasions or cuts, which have the effect of lowering the threshold. If none was found the fingers were placed in the electrodes. The subject was made as comfortable as possible, since the near-threshold shocks were difficult to report and were often confused with pulse throbs. The method of minimal changes was employed. The instructions were similar to those of Miles,[3a] except that the word "current" was used instead of "shock" in order to allay the suspicions of patients who might believe the procedure would injure them. After a practice session of five minutes, if the patient was cooperating satisfactorily and reporting shocks only when the current was actually applied to him, and if there seemed to be fair consistency between successive thresholds, forty determinations were made, twenty descending and twenty ascending. This took from fifteen to twenty minutes. Step intervals of 8 volts were used, and after every second ascending series the voltage was started at some value which halved the preceding ones.

An attempt was made to determine the thresholds of sixty-four patients, but only twenty-two cooperated sufficiently on the two examinations at an interval of three months for valid thresholds to be obtained.

The numbers in each subtype were: paranoid, 6; hebephrenic, 2; catatonic, 4; simple, 1; indeterminate, 2; mixed, 2 and unclassified, 5.

The mean age of the patient group was 30.6±1.44 with a standard deviation of 8.25±1.0. This group had a mean period of hospitalization (taken from the date of first admission) of 1.6±0.18 years with a standard deviation of 1.05±1.03.

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3. (*a*) Benedict, F. G.; Miles, W. R.; Roth, P., and Smith, H. M.: Human Vitality and Efficiency under Prolonged Restricted Diet, Washington, D. C., Carnegie Institution of Washington, 1919, pp. 176 and 611. (*b*) Erlanger, J., and Garrey, W. E.: Faradic Stimuli, Am. J. Physiol. **35**:377, 1914.

4. Certain modifications of the Miles arrangement were made. The noise caused by the gravity pendulum was eliminated by placing the pendulum in another room. By means of a small light, which flashed two seconds before the pendulum fell, the experimenter could prepare the observer by the usual "Ready-now!" A thermostatically-controlled water bath held the temperature of the electrode between 31 and 32 C. at the beginning of each session. This temperature was found to increase from 1 to 3 degrees while the threshold was being determined, owing to heat from the fingers. The electrode unit was placed so that the observer faced the experimenter, with a cardboard screen shielding the voltage control unit from the observer's view. Miles reported his current duration as 0.0035 second. After the experiment had been completed, we had the opportunity to measure our current duration by means of an oscillograph. It was found to be 0.016 second.

The normal male group (twenty-eight), which was selected from among hospital employees, had an age range comparable to that of the schizophrenic group, the mean being 30.6±1.22 and the standard deviation 7.30±0.93. The schizophrenic group is unrepresentative of schizophrenia in general.[5]

RESULTS

The principal results are presented in the tables. From table 1 it is apparent that the means and variation of the psychotic population as compared with the normal population are similar.[6] The statistically insignificant fall of the patients' mean on retest is probably due to a slower rate of adjustment to new situations in persons with schizo-

TABLE 1.—*Distribution of Means of Individual Thresholds in Volts* *

	Minimum	Maximum	Range	Mean	Standard Deviation of Distribution	Coefficient of Variation, per Cent
Patients						
Test I.....	61	174	113	110 ± 5.7	26.8 ± 4.1	24
Test II.....	55	156	101	102 ± 5.0	23.1 ± 3.5	23
Normal subjects						
Test I.....	65	164	99	101 ± 4.6	24.1 ± 3.2	24
Test II.....	60	188	128	103 ± 4.7	24.6 ± 3.3	24
Distribution of Standard Deviations of Individual Thresholds						
Patients						
Test I.....	6.9	20.0	13.1	10.9 ± 0.8	3.6 ± 0.5	33
Test II.....	4.4	17.5	13.1	9.4 ± 0.8	3.7 ± 0.6	39
Normal subjects						
Test I.....	4.5	20.8	16.3	9.5 ± 0.8	4.2 ± 0.6	44
Test II.....	4.7	30.8	26.1	9.6 ± 0.9	4.9 ± 0.7	51

* This table shows the marked similarity in the means and variation in both groups and in individual variation. The slightly higher coefficient of variation within the normal subjects is due to two extreme cases. The values which attach to the means and standard deviations are standard errors.

phrenia, an interpretation which is consistent with one drawn from a large series of unpublished observations on the motor behavior of persons with schizophrenia. The variation within the schizophrenic person as compared with that within the normal person likewise shows no significant difference.

An analysis of the interval between the descending and ascending series was carried out because it might be that a characteristic of schizophrenic subjects is the inability to maintain a given set as long as normal subjects, so that as the experiment progressed the interval between the descending series and the ascending series would widen or would

5. Hoskins, R. G.; Sleeper, F. H.; Shakow, D.; Jellinek, E. M.; Looney, J. M., and Erickson, M. H.: A Cooperative Research in Schizophrenia, Arch. Neurol. & Psychiat. **30**:388, 1933.

6. For sixty-three normal subjects Miles [3a] reported a mean of 117.3 volts, with a standard deviation of 30. This higher mean may be due to the shorter duration of current which Miles used—0.0035 second.

show greater fluctuations. Also, since Grabfield employed only an ascending series, a comparison of the normal and abnormal groups in this respect might yield a difference.

TABLE 2.—*Direct Current Thresholds in Volts* *

Trial	Minimum	Maximum	Range	Mean	Standard Deviation	Coefficient of Variation
			Patients (First Test)			
1	58	164	106	97 ± 5.6	25.5 ± 3.9	26
2	52	172	120	104 ± 6.1	27.8 ± 4.2	27
3	62	164	102	102 ± 5.8	26.4 ± 4.0	26
4	52	164	112	107 ± 6.2	28.5 ± 4.3	27
5	56	180	124	105 ± 6.3	28.9 ± 4.4	28
6	54	168	114	109 ± 6.2	28.6 ± 4.4	27
7	46	188	142	106 ± 6.7	30.9 ± 4.7	28
8	52	164	112	110 ± 5.9	27.1 ± 4.1	25
9	50	180	130	108 ± 6.5	29.7 ± 4.5	27
10	50	176	126	113 ± 7.0	32.3 ± 4.9	29
11	54	168	114	105 ± 6.0	27.4 ± 4.2	26
12	52	172	120	111 ± 6.5	29.6 ± 4.5	27
13	64	184	120	112 ± 6.6	30.2 ± 4.6	27
14	58	168	110	115 ± 6.3	28.9 ± 4.4	25
15	64	188	124	113 ± 6.2	28.6 ± 4.4	25
16	68	198	130	118 ± 6.4	29.5 ± 4.5	25
17	68	176	108	113 ± 5.9	27.0 ± 4.1	24
18	72	176	104	120 ± 5.7	26.2 ± 4.0	22
19	84	188	104	119 ± 6.3	28.9 ± 4.4	24
20	68	172	104	121 ± 5.8	26.6 ± 4.1	22
			Normal Subjects (First Test)			
1	56	128	92	91 ± 3.3	16.9 ± 2.3	19
2	40	136	96	94 ± 4.5	23.4 ± 3.2	25
3	52	136	84	91 ± 3.6	18.7 ± 2.5	20
4	40	150	110	96 ± 5.0	25.8 ± 3.5	27
5	60	140	80	96 ± 3.8	19.5 ± 2.6	20
6	44	152	108	98 ± 5.3	27.3 ± 3.7	28
7	60	156	96	97 ± 4.3	22.3 ± 3.0	23
8	60	168	108	100 ± 5.4	27.9 ± 3.8	28
9	60	160	100	100 ± 4.4	23.1 ± 3.1	23
10	52	164	112	100 ± 5.3	27.6 ± 3.7	28
11	56	168	112	100 ± 4.7	24.2 ± 3.3	24
12	60	180	120	104 ± 5.5	28.8 ± 3.9	28
13	68	176	108	101 ± 4.9	25.3 ± 3.4	25
14	60	180	120	105 ± 5.6	29.0 ± 3.9	28
15	64	176	112	102 ± 4.9	25.4 ± 3.4	25
16	60	184	124	105 ± 5.7	29.4 ± 4.0	28
17	64	188	124	102 ± 4.9	25.4 ± 3.4	25
18	64	188	124	107 ± 5.7	29.6 ± 4.0	28
19	68	176	108	106 ± 4.9	25.7 ± 3.5	24
20	68	184	116	108 ± 6.1	31.6 ± 4.3	29

* Tables 2 and 3 present direct current thresholds, trial by trial, for patients and normal subjects on two examinations. No significant trends or fluctuations peculiar to either group can be noted. The rise of the threshold with time is apparent. The values which attach to the means and standard deviations are standard errors.

On the first test the patients started with an interval of 13 volts on the first trial, fluctuated in a random fashion and ended on the twentieth trial with an interval of 12. For the second test, the first trial yielded a value of 10 volts and the last of 14. The normal group's interval on the first trial, first test, was 9; on the last trial, 12; for the second test these figures were 10 and 11. The mean interval for both groups is 12 volts for both tests. In no test or group was any trend distinguishable in either the descending or the ascending series.

In tables 2 and 3 are found frequency distribution constants on successive thresholds. The great similarity of the two groups is evident. The approximately equal rise of the threshold with time in both groups may be due to an increased skin or subcutaneous apparent resistance (apparent resistance is used here to include both true resistance and

TABLE 3.—*Direct Current Thresholds in Volts*

Trial	Minimum	Maximum	Range	Mean	Standard Deviation	Coefficient of Variation
			Patients (Second Test)			
1	60	148	88	96 ± 4.7	21.4 ± 3.3	22
2	52	144	92	97 ± 5.3	24.4 ± 3.7	25
3	56	160	104	98 ± 5.0	23.0 ± 3.5	24
4	48	152	104	99 ± 6.3	28.7 ± 4.4	29
5	60	156	96	98 ± 5.2	23.7 ± 3.6	24
6	52	168	116	100 ± 6.2	28.3 ± 4.3	28
7	64	172	108	103 ± 4.9	22.5 ± 3.4	22
8	44	152	108	100 ± 5.8	26.7 ± 4.1	27
9	60	164	104	101 ± 5.3	24.2 ± 3.7	24
10	44	156	112	104 ± 6.0	27.4 ± 4.2	26
11	56	168	112	103 ± 5.3	24.2 ± 3.7	23
12	40	144	104	106 ± 6.0	27.3 ± 4.2	26
13	60	164	104	103 ± 5.0	23.1 ± 3.5	22
14	52	160	108	105 ± 5.8	26.7 ± 4.1	25
15	56	168	112	103 ± 5.4	24.8 ± 3.8	24
16	48	152	104	105 ± 5.8	26.6 ± 4.1	25
17	68	160	92	105 ± 5.1	23.5 ± 3.6	22
18	52	144	92	106 ± 5.5	25.3 ± 3.9	24
19	68	164	96	104 ± 5.0	23.0 ± 3.5	22
20	52	152	100	106 ± 5.7	26.3 ± 4.0	25
			Normal Subjects (Second Test)			
1	40	152	112	94 ± 4.2	21.8 ± 2.9	23
2	52	164	112	98 ± 4.6	24.1 ± 3.2	25
3	48	160	112	97 ± 4.3	22.6 ± 3.0	23
4	52	188	136	102 ± 5.1	26.5 ± 3.6	26
5	52	168	116	99 ± 4.4	22.7 ± 3.1	23
6	48	176	128	101 ± 5.1	26.3 ± 3.5	26
7	52	184	132	99 ± 4.8	24.9 ± 3.4	25
8	48	192	144	103 ± 5.6	28.9 ± 3.9	28
9	56	180	124	100 ± 4.8	24.8 ± 3.3	25
10	44	196	152	104 ± 5.8	29.9 ± 4.0	29
11	52	196	144	101 ± 5.3	27.6 ± 3.7	27
12	60	208	148	108 ± 5.8	30.0 ± 4.0	28
13	60	200	140	103 ± 5.1	26.7 ± 3.6	25
14	56	184	128	106 ± 5.2	27.0 ± 3.6	25
15	64	200	136	106 ± 5.2	27.2 ± 3.7	26
16	60	200	140	108 ± 5.5	28.4 ± 3.8	26
17	64	200	136	106 ± 5.2	27.1 ± 3.7	26
18	60	202	142	109 ± 5.6	29.0 ± 3.9	27
19	64	188	124	105 ± 4.8	25.2 ± 3.4	24
20	56	212	156	110 ± 5.9	30.6 ± 4.1	28

counter electromotive force), altered skin capacity, receptor fatigue and adaptation.

Some other points brought out by this study are worthy of mention. In the patients, the test-retest correlation was 0.58 ± 0.14 and in the normal subjects, 0.83 ± 0.06. The lower correlation in the patients is probably due to the adjustment factor mentioned earlier, especially to those whose thresholds fell enough to lower the mean of the whole population. Scatter diagrams of age versus mean threshold, and of time of

day versus mean threshold [7] in the normal subjects and the patients, and period of hospitalization versus mean threshold in patients failed to indicate a relationship between these factors.

The shocks were generally localized by the subjects in the finger-tips below the level of the saline solution. Some placed the sensations along the sides of the fingers or in the joints. The most frequent qualitative report was that of a prickly sensation, and now and then a sensation like that of a muscle twitching.

Failure to confirm previous results may be explained on several grounds. Faradic break shock stimuli, which rise rapidly to their full value and then die away more slowly, are different from direct current stimuli of rectangular wave form and constant duration of time. Our reason for not working with faradic stimuli, as previously mentioned, was based on the fact that as one varied shock intensity the induced wave form changed.[8]

Another possibility which might explain the difference between our results and those of Grabfield is that in his subjects (at the Boston Psychopathic Hospital) the psychosis was of more recent onset; high

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7. Grabfield, G. P., and Martin, E. G.: Variations in the Sensory Threshold for Faradic Stimulation in Normal Human Subjects: I. The Diurnal Rhythm, Am. J. Physiol. **31**:300, 1913. Martin, E. G.; Bigelow, G. H., and Wilbur, G. B.: Variations in the Sensory Threshold for Faradic Stimulation in Normal Human Subjects: II. The Nocturnal Variation, ibid. **33**:415, 1914.

8. If one can obtain differences with the two types of stimuli between a normal and a schizophrenic group, many problems will be suggested which will involve current intensity, duration and wave form as well as skin resistance, capacity and polarization effects. The skin (an individual variable) itself introduces important modifications in current wave form, as Gildemeister (Ueber elektrische Schwingungen, hervorgerufen durch die Hautkapatzität, Arch. f. d. ges. Physiol. **219**:82, 1928) has shown for faradic currents, and Strohl (La conductibilité électrique du corps humain, Paris, Masson et Cie, 1925), Fabre and Swyngedauw (Enrégistrement oscillographique du courant de polarization du corps humain, Compt. rend. Soc. de biol. **104**:560, 1930), and Hōzawa (Studien über die Polarisation der Haut, Arch. f. d. ges. Physiol. **219**:111, 1928) for direct current. Especially suggestive for threshold purposes is Rein's paper (Die Gleichstrom-Leiter-Eigenschaften und elektromotorischen Kräfte der menschlichen Haut und ihre Auswertung zur Untersuchung von Funktionszuständen des Organes, Ztschr. f. Biol. **85**:232, 1927), which relates polarization potential and pain. This list is not exhaustive, and the reader may consult Evans (Recent Advances in Physiology, ed. 4, Philadelphia, P. Blakiston's Son & Co., 1930, pp. 280-339), Landis and De Wick (The Electrical Phenomena of the Skin [Psychgalvanic Reflex], Psychol. Bull. **26**:64, 1929) and Landis (The Electrical Phenomena of the Skin, Psychol. Bull. **29**:693, 1932). Indeed it is doubtful whether one can make statements about "general nervous irritability" unless measurements of the peripheral factors accompany the threshold data. More extended investigation of the problem is not planned at the present time, however, because of the high incidence of insufficient cooperation in a representative schizophrenic group.

thresholds may have been present in one half of those patients. It is further stated that the Psychopathic Hospital has an error of 20 per cent in classificatory diagnosis,[1a] whereas in our group the the diagnosis has been repeatedly confirmed. This may account partially for the divergent results. Finally, the difference in the number of observations taken for statistical purposes and the difference in the degree of experimental control used in prior work as compared with mine are probably important factors contributing to the discrepancy.

SUMMARY

As a check on the statement that high faradic current thresholds are found in about 50 per cent of patients with dementia praecox, a technic of direct current stimulation was employed. This revealed no significant differences between a schizophrenic group and a comparable normal one in the means of the two groups, the scatter about the mean, the mean variation within individual persons, the interval between the ascending and descending series and the course of the threshold. A slight nonsignificant difference between the means of the two groups was found on the first test, which disappeared on the second test. This is interpreted as indicating a slower rate of adjustment to new situations by the patients than by normal subjects. Reasons for the failure to confirm Grabfield's results are advanced.

Ruth McNitt computed the statistical constants.

CHEMICAL CHANGES IN THE BLOOD INDUCED BY HYPERPYREXIAL BATHS

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The frequent occurrence of clinical signs of tetany and of the major manifestations of epilepsy in patients subjected to hyperpyrexial baths has aroused interest in the chemical changes resulting from this procedure. Profound physiologic and chemical responses within the body occur, being closely interdependent in origin and in effect. The present investigation deals entirely with the chemical and water-shifting effects of hyperpyrexial baths, giving attention particularly to those changes having some bearing on the functional activity of the nervous system.

On exposure to hot baths, the human organism responds with hyperventilation of the lungs in an attempt to cool the body.[1] This has the effect of removing carbonic acid from the blood in the "blowing off" of abnormal amounts of carbon dioxide in the expired air, and creates the state designated as uncompensated deficit of carbon dioxide. This fact was demonstrated for hot baths as early as 1905 by Haldane and Priestley,[2] and was later confirmed by a number of workers.[3] Mosso [4] named the condition of reduced carbon dioxide content of the blood "acapnia," and found it to appear following pulmonary hyperventilation from any cause.[5] Actual measurements of the carbon dioxide

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With the technical assistance of Rita Canessa.

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Supported in part by the Rockefeller Fluid Research Fund of the Stanford University Medical School.

Conducted under the guidance of the late Dr. Henry George Mehrtens, Professor of Neuropsychiatry, Stanford University.

1. Adolph, E. F., and Fulton, W. B.: Am. J. Physiol. **67**:573, 1924.

2. Haldane, J. B. S., and Priestley, J. G.: J. Physiol. **32**:252, 1905.

3. (*a*) Hill, L., and Flack, M.: J. Physiol. **38**:lvii, 1909. (*b*) Graham, G., and Poulton, E. P.: Quart. J. Med. **6**:82, 1912-1913. (*c*) Haggard, H. W.: J. Biol. Chem. **44**:131, 1920. (*d*) Barbour, H. G.: Physiol. Rev. **1**:295, 1921. (*e*) Bazett, H. C., and Haldane, J. B. S.: J. Physiol. **55**:iv, 1921. (*f*) Bazett, H. C.: Am. J. Physiol. **70**:412, 1924. (*g*) Landis, E. M., and others: ibid. **76**:35, 1926. (*h*) Adolph and Fulton.[1]

4. Mosso, A.: Arch. ital. de biol. **42**:192, 1904; **43**:216, 1905.

5. (*a*) Henderson, Y.: Am. J. Physiol. **25**:310, 1909-1910. (*b*) Henderson, Y.; Prince, A. L., and Haggard, H. W.: J. Pharmacol. & Exper. Therap. **11**:203, 1918. (*c*) Henderson, Y., and Haggard, H. W.: J. Biol. Chem. **33**:333 and 355, 1918. (*d*) Davies, H. W.; Haldane, J. B. S., and Kennaway, E. L.: J. Physiol. **54**:32, 1920. (*e*) Collip, J. B., and Backus, P. L.: Am. J. Physiol. **51**:568, 1920. (*f*) Grant, S. B., and Goldman, A.: ibid. **52**:209, 1920.

content of the arterial and venous blood have shown a decided fall in values;[6] for example, the carbon dioxide content of the arterial blood was found by Landis and his associates[3g] to be 54.9 per cent by volume before the bath and 37.9 per cent by volume after the bath.

The loss of carbon dioxide from the blood is of such a degree as to give rise gradually to a condition of alkalosis, which may be detected without difficulty in rising p_H values.[7] The reported increase in p_H has varied between 0.12 and 0.33 point among the different authors, a marked rise when presented in terms of p_H.

An important compensatory mechanism is brought into action with the development of the states of acapnia and alkalosis. A shifting of alkali, chiefly bicarbonate ions, out of the blood occurs, in order to reduce its alkalinity. Two avenues of escape for the bicarbonate ions are thought to exist, one into the tissues[8] and the other into the urine via the kidneys.[9] Definite proof of the escape of these ions is found in the measurable reduction in the alkali reserve of the plasma.[10]

It was noted some years ago[11] that at any given saturation of hemoglobin with oxygen, oxygen tension becomes lowered as the carbon dioxide tension is lowered. Many authors agree, therefore, that in the presence of the acapnia of pulmonary hyperventilation overstability of the oxyhemoglobin creates a functional anoxemic condition. Early writers attributed the nervous symptoms of hyperpnea to oxygen-want within the tissues.

As time progressed, a controversy arose in the literature regarding the relative importance of the coexistent states of alkalosis and anoxemia in the production of the nervous and mental symptoms associated with overventilation of the lungs. Those who have attributed primary impor-

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6. (*a*) Ewald, A.: Arch. f. d. ges. Physiol. **7**:580, 1873. (*b*) Haggard.[3e] (*c*) Flinn, F. B., and Scott, E. L.: Am. J. Physiol. **66**:191, 1923. (*d*) Adolph and Fulton.[1] (*e*) Bischoff, F.; Long, M. L., and Hill, E.: J. Biol. Chem. **90**:321, 1931. (*f*) Landis and others.[3g]

7. Cajori, F. A.; Crouter, C. Y., and Pemberton, R.: J. Biol. Chem. **57**:217, 1923. Haggard.[3e] Flinn and Scott.[6c] Landis and others.[3g] Bischoff, Long and Hill.[6e]

8. Henderson and Haggard.[5c] Collip and Backus.[5e]

9. (*a*) Hasselbalch, K. A.: Biochem. Ztschr. **46**:403, 1912. (*b*) Leathes, J. B.: Brit. M. J. **2**:165, 1919. (*c*) Davies, Haldane and Kennaway.[5d] (*d*) Collip and Backus.[5e] (*e*) Grant and Goldman.[5f] (*f*) Bazett and Haldane.[3e] (*g*) Greenwald, I.: J. Biol. Chem. **54**:285, 1922. (*h*) Koehler, A. E.: Acid-Base Equilibrium: Clinical Studies in Alkalosis, Arch. Int. Med. **31**:590 (April) 1923. (*i*) Bazett.[3f] (*j*) Bazett, H. C., and others: Am. J. Physiol. **70**:430, 1924. (*k*) Adolph and Fulton.[1] (*l*) Landis and others.[3g] (*m*) Bischoff, Long and Hill.[6e]

10. Haggard.[3e] Davies, Haldane and Kennaway.[5d] Collip and Backus.[5e] Grant and Goldman.[5f] Flinn and Scott.[6c] Adolph and Fulton.[1]

11. Grant, S. B.: Am. J. Physiol. **66**:274, 1923.

tance to the anoxemia have reported objective relief from symptoms after the breathing of pure oxygen or mixtures of air and oxygen.[12] Of more recent origin has been the belief that the alkalosis per se is responsible for the symptoms developed.[13] The breathing of carbon dioxide or the rebreathing of expired air was shown to alleviate the tetanic and the mental symptoms.

It has been known for many years that changes in the water content of the blood follow exposure to high environmental temperatures. Matthes [14] reviewed the literature on this subject in 1900. The blood volume had been shown to increase, as evidenced by the diminution in the hemoglobin concentration, red blood cell count and viscosity of the blood. Exposure to cold had the opposite effect. Barbour [15] has, during the past decade, revived this observation in his investigations dealing with fever. When dogs were subjected to hot baths at 40 C., the dilution of the blood was found roughly to amount to 10 per cent. About this fact he was led to build his conception of water-shifting between the tissues and the blood as a protection of the body against overheating. By this means larger quantities of blood were made available for filling the greatly dilated peripheral vascular bed, bringing more blood to the surface of the body for direct conduction and radiation of heat, as well as mobilizing water for loss of heat through evaporation of the sweat. A great deal of work has appeared in the literature confirming Barbour's work.[16] Water-shifting was shown by Barbour and Tolstoi [16d] to be accomplished through the functioning of the central nervous system, for in dogs in which successful decerebration and transection of the cord had been performed this response to high external temperatures had been lost. The work of Henderson, Prince and Haggard [5b] had shown five years earlier that dilution of the blood resulted from

12. Hill and Flack.[8a] Henderson.[5a] Davies, Haldane and Kennaway.[5d] Bazett and Haldane.[3e] Macleod, J. J. R.: Physiology and Biochemistry in Modern Medicine, ed. 4, St. Louis, C. V. Mosby Company, 1922, p. 381. Greenwald.[9g] Morris, N.: Brit. J. Exper. Path. **3**:101, 1922. Uyeno, K.: J. Physiol. **57**:203, 1923. Adolph and Fulton.[1] Bischoff, Long and Hill.[6e] Bazett.[3f]

13. Henderson and Haggard.[5c] Collip and Backus.[5e] Grant and Goldman.[5f] Grant.[11] Adolph and Fulton.[1] Landis and others.[3g]

14. Matthes, Max: Lehrbuch der klinischen Hydrotherapie für Studierende und Aerzte, Jena, Gustav Fischer, 1900.

15. Barbour, H. G.: Proc. Soc. Exper. Biol. & Med. **18**:186, 1920-1921.

16. (*a*) Barcroft, J., and others: Phil. Tr. Roy. Soc., 1922, pp. 211, 352 and 455. (*b*) Lozinsky, E.: Am. J. Physiol. **67**:388, 1924. (*c*) Bazett and others.[9j] (*d*) Barbour, H. G., and Tolstoi, E.: Am. J. Physiol. **67**:378, 1924. (*e*) Barbour, H. G.; Loomis, N. M.; Franklin, R. W., and Warner, J. H.: J. Physiol. **59**:300, 1924. (*f*) Hamilton, W. F.; Barbour, H. G., and Loomis, N. M.: ibid. **59**:306, 1924. (*g*) Barbour, H. G., and Hamilton, W. F.: Am. J. Physiol. **73**: 315, 1925. (*h*) Barbour, H. G.; Dawson, M. H., and Neuwirth, I.: ibid. **74**:204, 1925.

pulmonary hyperventilation without the influence of heat; furthermore, that the diminution in hemoglobin could be directly correlated with the depth of the acapnia. The chemical influences in water-shifting within the body were thereby made more clear. In view of the analogous chemical states developed during simple voluntary hyperpnea and hyperpyrexial baths, the observed changes in water balance may be developed primarily on a chemical basis.

After exposure for approximately one hour to high temperatures, dilution of the blood gives place to concentration following the loss of water from the body in the pulmonary air,[3c] sweat [17] and urine.[18] This concentration of the blood amounts to between 10 and 16 per cent.[19]

With the migration of water into the blood, it has been shown that a protein-rich fluid flows from the tissues into the blood.[20] The source of this protein-salt solution was thought by Barbour [3d] to be chiefly the muscles. Erlanger [21] observed that whenever fluid enters the blood stream, crystalloids and proteins of the same concentration as the tissue fluids flow in with it. Barbour and his associates [16e, h] detected only a slight decrease in the total blood solids accompanying a fall of 10 per cent in the hemoglobin concentration, indicating to them that migration of tissue solids into the blood had taken place.

Exposure to hyperpyrexial baths has a stimulating effect on sugar metabolism, as measured by the rise in the respiratory quotient and the fall in the blood sugar level.[22] It is the general opinion of investigators that the augmented body metabolism of fever is responsible for the lowering of the blood sugar values. Alkalosis from bicarbonate feeding has been shown by Macleod and others [23] to effect a lowering of the

17. (*a*) Barbour.[3d] (*b*) Sutton, H.: J. Path. & Bact. **13**:62, 1908-1909. (*c*) Bazett and Haldane.[3e] (*d*) Bazett, H. C.: Circulation in Pyrexia, J. A. M. A. **97**:1271 (Oct. 31) 1931. (*e*) Bazett.[3f] (*f*) Barbour, Dawson and Neuwirth.[16h]

18. Graham and Poulton.[3b] Bazett and Haldane.[3e] Adolph and Fulton.[1] Bazett.[3f] Landis and others.[3g] Davies, Haldane and Kennaway.[5d] Collip and Backus.[5e] Bazett and others.[9j]

19. Haldane, J. B. S.: J. Hyg. **5**:494, 1905. Barbour.[15] Bazett and Haldane.[3e] Flinn and Scott.[6c] Bazett.[3f] Bischoff, Long and Hill.[6e] Underhill, F. P., and Pack, G. T.: Am. J. Physiol. **66**:520, 1923.

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blood sugar. The alkalosis of hyperpyrexial baths may therefore exert some influence on the reduction in the blood sugar level.

Investigations dealing with the inorganic ions of the blood under the present experimental conditions were not to be found in the literature.

EXPERIMENTAL STUDIES

Experimental Procedure.—The purpose of the present study was to determine the chemical response of the body to hyperpyrexial baths, keeping in mind those changes favoring neuromuscular hyperirritability, such as alkalosis, disturbed water balance, hypoglycemia and low calcium and high phosphorus levels, because of their bearing on the functional activity of the nervous system. Twelve young adult subjects were chosen because of the minor character of their complaints and the absence of organic disease, thus insuring a relatively normal state of blood chemistry.

Specimens of blood were taken just before the bath while the patient was still in bed and again at the height of the febrile reaction in the bath. The body temperature was increased as rapidly as possible to between 105 and 106 F. within from thirty to forty-five minutes. The maximum physiologic and chemical responses were observed at the peak of body temperature; consequently this period was selected for investigation and comparison with the normal state of blood chemistry before the bath.

The blood was analyzed for p_H, carbon dioxide-combining power, hemoglobin concentration, serum protein (albumin and globulin fractions), whole blood sugar, serum sodium, serum inorganic phosphorus and serum calcium (total and diffusible fractions).

Methods.—The p_H determinations were made according to the colorimetric method of Hastings and Sendroy,[24] and the alkali reserve by the method of Van Slyke.[25] The Sahli method was used for the determination of hemoglobin concentration. The albumin and globulin fractions of the serum protein were determined colorimetrically by the technic of Greenberg.[26] Folin's modification[27] of the Folin-Wu method was employed for whole blood sugar. The serum sodium was measured by the iodometric method of Kramer and Gittleman.[28] The Gunther and Greenberg[29] modification of the Fiske and Subbarow[30] method for serum inorganic phosphorus was employed. The total serum calcium was determined by the Clark and Collip[31] procedure, as modified slightly by Kirk and Schmidt.[32] The diffusible serum calcium was determined by the Greenberg and Gunther method.[33]

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TABLE 1.—*Chemical Analyses of the Blood Before and During Hyperpyrexial Baths*

	Plasma *pH*	Carbon Dioxide-Combining Power, per Cent by Volume	Serum Globulin, Gm. per 100 Cc.	Serum Albumin, Gm. per 100 Cc.	Total Serum Protein, Gm. per 100 Cc.	Serum Inorganic Phosphorus, Mg. per 100 Cc.	Serum Calcium, Diffusible, Mg. per 100 Cc.	Serum Calcium, Mg. per 100 Cc.	Serum Sodium, Mg. per 100 Cc.	Whole Blood Sugar, Mg. per 100 Cc.	Hemoglobin (Sahli) per Cent
S. G., male (3/16/32)											
Before bath	7.38	54.92	2.22	4.81	7.03	4.30	6.61	11.50	.....	.....	..
At height of bath	7.45	48.26	2.38	5.06	7.44	4.74	6.17	11.12	.....	.....	..
Degree of change	+0.07	—6.66	+0.16	+0.25	+0.41	+0.44	—0.44	—0.38	.....	.....	..
H. G., female (4/12/32)											
Before bath	7.38	54.10	2.49	4.56	7.05	3.42	5.87	10.05	316.50	111.60	..
At height of bath	7.53	48.52	2.57	4.65	7.22	3.37	5.73	9.80	316.50	112.10	..
Degree of change	+0.15	—5.58	+0.08	+0.09	+0.17	—0.05	—0.86	—0.25	0.0	+0.50	..
H. W., female (4/14/32)											
Before bath	7.41	58.84	2.61	4.45	7.06	2.96	5.68	11.75	316.50	189.30	86
At height of bath	7.50	49.82	2.53	4.21	6.74	3.13	5.15	10.44	313.00	140.40	82
Degree of change	+0.09	—9.02	—0.08	—0.24	—0.32	+0.17	—0.53	—1.29	—3.50	—48.90	—4
M. B., female (4/14/32)											
Before bath	7.38	58.84	2.57	4.27	6.84	6.67	4.31	7.50	337.30	126.20	90
At height of bath	7.47	55.94	2.64	4.21	6.85	7.15	4.11	6.84	331.50	120.70	83
Degree of change	+0.09	—2.90	+0.07	—0.06	+0.01	+0.48	—0.20	—0.66	—5.80	—5.50	—7
M. R., female (4/21/32)											
Before bath	7.40	51.93	2.38	4.34	6.72	2.95	5.25	10.25	327.50	81.30	82
At height of bath	7.48	49.00	2.38	4.55	6.93	3.17	5.09	10.25	319.00	70.70	76
Degree of change	+0.08	—2.93	0.0	+0.21	+0.21	+0.22	—0.16	0.0	—8.50	—10.60	—6
W. T., male (4/22/32)											
Before bath	7.41	55.31	2.33	5.05	6.38	3.88	6.25	10.62	.....	97.00	94
At height of bath	7.52	52.31	2.38	5.34	6.72	3.80	4.95	10.15	.....	108.10	86
Degree of change	+0.11	—3.00	+0.05	+0.29	+0.34	—0.08	—1.30	—0.47	.....	+11.10	—8
G. F., female (4/25/32)											
Before bath	7.40	58.81	2.53	4.47	7.00	4.43	4.92	10.85	329.00	113.00	88
At height of bath	7.43	53.08	2.64	4.55	7.19	4.59	5.15	10.82	326.50	112.30	81
Degree of change	+0.03	—5.73	+0.11	+0.08	+0.19	+0.16	+0.23	—0.03	—2.50	—0.70	—7
V. T., female (4/26/32)											
Before bath	7.41	57.09	2.91	4.35	7.26	4.05	5.75	11.00	329.00	94.90	..
At height of bath	7.55	52.44	3.03	4.32	7.35	4.28	5.75	11.10	332.00	84.80	..
Degree of change	+0.14	—4.65	+0.12	—0.03	+0.09	+0.23	0.00	+0.10	+3.00	—10.10	..
De V., male (5/3/32)											
Before bath	7.40	55.52	2.47	4.38	6.85	3.39	6.00	12.40	315.00	110.60	..
At height of bath	7.50	52.59	2.77	4.92	7.69	3.00	6.02	12.50	303.70	90.50	..
Degree of change	+0.10	—2.93	+0.30	+0.54	+0.84	—0.39	+0.02	+0.10	—11.30	—20.10	..
B. P., female (5/4/32)											
Before bath	7.41	57.81	3.43	4.94	8.37	3.30	5.87	10.90	306.70	125.00	..
At height of bath	7.45	47.38	3.33	4.67	8.00	3.00	5.88	11.12	300.00	93.00	..
Degree of change	+0.04	—10.43	—0.10	—0.27	—0.37	—0.30	+0.01	+0.22	—6.70	—32.00	..
Rev. O., male (5/16/32)											
Before bath	7.39	60.58	2.23	4.59	6.82	3.12	5.80	11.19	315.10	98.90	89
At height of bath	7.55	52.96	2.35	4.61	6.96	3.23	5.80	11.34	313.90	90.60	82
Degree of change	+0.16	—7.62	+0.12	+0.02	+0.14	+0.11	0.00	+0.15	—1.20	+11.70	—7
H. P., female (1/9/32)											
Before bath	7.52	58.90	2.38	3.81	6.19	3.31	7.94	9.80	319.70	.....	..
At height of bath	7.54	54.10	2.69	4.15	6.84	4.10	7.35	8.33	319.70	.....	..
Degree of change	+0.02	—4.80	+0.31	+0.34	+0.65	+0.79	—0.59	—1.47	0.00	.....	..

RESULTS AND COMMENTS

The results of the chemical analyses are summarized in tables 1 and 2. The p_H values of the blood were found to rise between 0.02 and 0.16 point, the average for all cases being 0.09 point, indicating a well defined state of alkalosis. The alkali reserve of the plasma decreased on the average 9.37 per cent from the original control values. The removal of sodium bicarbonate from the blood in the presence of alkalosis is a compensatory mechanism to accomplish a reduction in the basic content of the blood. The serum proteins were found to increase, even in the presence of a measurable degree of dilution of the blood, falling in line with previous reports in the literature. The globulin fraction increased slightly more than the albumin, averaging an increase of 3.74 and 2.27 per cent, respectively. In close correspondence with the work

TABLE 2.—*Summary of Results*

	Average Values Before Bath	Average Degree of Change in Bath	Average Percentage of Change
Plasma p_H	7.407	+ 0.09	1.21 rise
Carbon dioxide-combining power, per cent by volume	58.88	— 5.52	9.37 fall
Serum globulin, Gm. per 100 cc	2.54	+ 0.095	3.74 rise
Serum albumin, Gm. per 100 cc	4.50	+ 0.102	2.27 rise
Total serum protein, Gm. per 100 cc	6.96	+ 0.197	2.83 rise
Serum inorganic phosphorus, mg. per 100 cc	3.55	+ 0.149	4.20 rise
Serum calcium, diffusible, mg. per 100 cc	5.99	— 0.235	3.92 fall
Serum calcium, total, mg. per 100 cc	10.94	— 0.331	3.03 fall
Serum sodium, mg. per 100 cc	319.40	— 3.65	1.14 fall
Whole blood sugar, mg. per 100 cc	112.78	—10.46	9.45 fall
Hemoglobin (Sahli), per cent	88.16	— 6.50	7.30 fall

of Barbour and others a dilution of the blood averaging 7.3 per cent, measured by hemoglobin values, was obtained. Whole blood sugar values showed an average fall of 9.45 per cent. Three factors could conceivably be functioning to lower the blood sugar values: (1) the increased metabolic activity of fever, (2) the alkalosis and (3) the dilution of the blood.

The inorganic constituents of the blood have shown rather significant trends during the course of hyperpyrexial baths. An average increase of 4.2 per cent over the control values was found in the serum inorganic phosphorus. This value assumed some significance when obtained at a time when the blood had undergone measurable dilution. The cause for the elevation in the inorganic phosphorus cannot be stated definitely, but may have had some dependence on the alkalosis and the augmented muscle metabolism of fever. A fall in the total serum calcium amounted to 3.03 per cent, and in the diffusible calcium, to 3.92 per cent. This may have been accomplished through the influence of: (1) dilution of the blood, (2) alkalosis, (3) an increase in blood proteins and (4) an increase in inorganic phosphorus. The tendency is to attribute impor-

tance to the decline in diffusible calcium values, particularly when obtained during the course of the developing neuromuscular hyperexcitability of the bath. A difference of opinion exists among authors with regard to the etiologic importance of the blood calcium concentration in alkalotic tetany;[34] however, the downward trend in calcium values falls in line with the usual cationic changes observed in the states of neuromuscular hyperexcitability. The serum sodium content was not appreciably altered, showing an average decrease of 1.14 per cent. The migration of salts from the tissues into the blood during the process of dilution of the blood served to maintain the sodium content of the serum at approximately the normal level.

SUMMARY

The major changes observed in the body as a result of hyperpyrexial baths, namely, alkalosis, water-shifting, hypoglycemia, rising inorganic blood phosphorus and falling blood calcium, have the general combined effect of exciting nerve tissue and have a definite influence on the appearance of the nervous and mental phenomena observed.

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Clinical Notes

RUPTURED ANEURYSM AT JUNCTION OF RIGHT ANTERIOR COMMUNICATING AND ANTERIOR CEREBRAL ARTERIES

Report of a Case with Resulting Subarachnoid Hemorrhage

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Several years ago, I had the opportunity to study three patients with spontaneous subarachnoid hemorrhage who had been admitted to the medical division of the Hospital of the University of Pennsylvania. In the publication which described these cases [1] it was stated that the word "spontaneous" excluded all subarachnoid hemorrhages resulting from recognizable causes—such as trauma, infection, either meningeal or occurring from infective emboli (so-called mycotic aneurysms), syphilis, arteriosclerosis, atheroma and blood dyscrasia—or produced accidentally by the rupture of a cyst with escape of blood into a lateral ventricle. It was emphasized that while at first thought it would seem probable that degenerative vascular disease would be found to be the commonest cause of subarachnoid hemorrhage, the age incidence in this disease and the absence of concomitant manifestations of cardiovascular disorders were convincing evidences that this was not true. In Neal's [2] series the average age of the patients in twenty cases was 27, and in Symonds' [3] series of one hundred and fourteen cases collected from the literature, including thirty-nine of undetermined etiology, the average age was 30.

Symonds [3] expressed the opinion that previous authors had not been sufficiently impressed by the possibility of aneurysm as a cause of this condition. He called attention to the writings of Sir William Gull,[4] who in 1859 stated: "Whenever young persons die with symptoms of ingravescent apoplexy and after death, large effusion of blood is found, especially if the effusion be over the surface of the brain in the meshes of the pia mater; the presence of an aneurysm is probable."

In 1930, Forbus [5] published his excellent treatise, entitled "On the Origin of Miliary Aneurysms of the Superficial Cerebral Arteries," which stands as a milestone in the study of the etiology and mode of development of intracranial aneurysms. The publication of Forbus resulted from an unusual opportunity to study the case of a Negro, aged 24, who at autopsy was found to have multiple small saccular

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1. Leopold, S. S.: Spontaneous Subarachnoid Hemorrhage, M. Clin. North America **13**:869 (Jan.) 1930.

2. Neal, Josephine: Spontaneous Meningeal Hemorrhage, J. A. M. A. **63**: 1362 (Oct. 17) 1914.

3. Symonds, C. P.: Spontaneous Subarachnoid Hemorrhage, Quart. J. Med. **18**:93, 1924.

4. Gull, William: Cases of Aneurysm of the Cerebral Vessels, Guy's Hosp. Rep. **5**:281, 1859.

5. Forbus, W. D.: On the Origin of Miliary Aneurysms of the Superficial Cerebral Arteries, Bull. Johns Hopkins Hosp. **47**:239, 1930.

aneurysms of the superficial cerebral arteries, with rupture of one of them into the subarachnoid space. Five aneurysms were present. The first originated at the oblique angle formed by the left anterior and the middle cerebral artery; the second, exactly at the bifurcation of the left middle cerebral artery; the third, at the fork formed by the branches of the left middle cerebral artery, and the fourth, which had ruptured, from that portion of the right anterior cerebral artery which helps to form the circle of Willis. The fifth was microscopic; it also was found at the fork produced by a dividing vessel. Microscopically, all of these aneurysms were essentially the same. There was nothing abnormal in the wall of the vessel from which the sac arose. Exactly at the point of origin, the intima was tremendously thickened, and the internal elastic lamina and the muscular coat disappeared abruptly and were not found anywhere in the aneurysmal sac. There was no evidence of any inflammatory process.

Studies were made in this case of other cerebral arteries, both at points in their length and at their bifurcations. In almost all of twenty sections made at points of bifurcation, "a peculiar defect in the muscularis was found exactly at the apex of the acute angle formed by the division of the vessel. In some, the media was replaced by connective tissue; in others, a considerable gap was seen in the muscularis. There was no inflammatory reaction and no necrosis. The connective tissue appeared to be a simple continuation of the overlying adventitia and had none of the characteristics of a scar. No abnormalities were found at points other than at the bifurcations. The location of the aneurysms corresponded exactly to the location of the muscularis defect."

Further studies of cerebral vessels unassociated with aneurysms showed medial defects at points of bifurcation in twenty-five of thirty-three cases. In regard to other arteries, such defects were found at a fork in two of nine cases in which the coronary vessels were studied and in about the same proportion in the mesenteric arteries.

Studies of the development of the aorta convinced Forbus that the peculiar defect in the vessel wall at the point of bifurcation dates from embryonic life and is found often enough, particularly in the brain, to be considered relatively normal. He was, further, able to demonstrate by a study of hydrostatics that the point of maximum intra-arterial pressure is at the point of the defect (at the bifurcation).

Therefore, if one accepts the results of this fundamental study, there is available for the first time a rational explanation of the frequency of intracranial aneurysms and of spontaneous subarachnoid hemorrhage in young persons.

In almost all of the published cases, intracranial aneurysms have occurred at or near the junction of the internal carotid artery and the circle of Willis. In such a case diagnosis was made and subsequently confirmed post mortem by Symonds, who was then a visitor at Cushing's clinic. Allbright was a student at Harvard University at that time, and his subsequent interest in these cases was initiated by Symonds' diagnosis. He [6] recently added two new cases to the literature and abstracted thirty others. In all of these cases aneurysms occurred at or near the junction of the internal carotid artery and the circle of Willis. The symptoms and signs are divided into those due to pressure by the aneurysm (neighborhood signs) and those due to leakage (subarachnoid hemorrhage).

In regard to neighborhood signs, Albright found that the third nerve was involved in every case. The fourth nerve and the ophthalmic branch of the fifth

6. Albright, Fuller: The Syndrome Produced by Aneurysm at or Near the Junction of the Internal Carotid Artery and the Circle of Willis, Bull. Johns Hopkins Hosp. **44**:215 (April) 1929.

nerve were frequently implicated. The sixth, seventh and eighth nerves were only rarely compressed. Subarachnoid hemorrhage occurred in fifteen of the thirty cases.

In case 29 of the series cited by Albright and originally reported by Woltman and Shelden,[7] there were two aneurysms: One, which had ruptured, was at the usual site, and the other, a small unruptured one, was at the junction of the anterior communicating arteries. The patient also had coarctation of the aorta and fetal lobulations in the kidneys. The location of the unruptured aneurysm was almost identical with that of the one found in my patient.

Albright speculated on the probable etiology of the aneurysms in these thirty cases and concluded that one resulted from an infected embolus, two were traumatic, three and possibly three more were due to syphilis, five and possibly five more resulted from atheroma, and thirteen and possibly two more were produced by congenital defects in the walls of the cerebral vessels.

The aneurysms resulting from congenital defects usually were found where a vessel divided or where a small branch was given off. Four patients had multiple aneurysms. Two had coarctation of the aorta, and two had other associated congenital deformities. In this group, the youngest patient was 18 and the oldest, 45.

Of this entire group, three patients were operated on. In one, the carotid artery was partially occluded by surrounding it with a double layer of fascia lata. Hemiplegia developed, and the patient died. The second patient was in good health five years after ligation of the common carotid artery, and the third obtained relief from a similar operation.

The patient whose case is reported here was admitted to the hospital with the typical clinical picture of spontaneous subarachnoid hemorrhage. The presence of intracranial aneurysm was not suspected because there were no localizing neurologic findings. This, of course, is to be explained by the unusual location of the aneurysm, in that it was not found near the junction of the internal carotid artery and the circle of Willis.

REPORT OF CASE

History.—E. R., a man, aged 43, was admitted to the service of Dr. Alfred Stengel at the Hospital of the University of Pennsylvania on Dec. 7, 1932, with the chief complaints of severe headache, nausea, vomiting and disorientation. He was well until Oct. 23, 1932, when he was found moaning on the floor. He was not unconscious but was disoriented. He appeared to have a severe headache. A few minutes later there occurred an attack of projectile vomiting. A few hours thereafter he was able to recognize his family. Severe headache, nausea and vomiting persisted. At the end of a week he was removed to a hospital outside Philadelphia; he was discharged one week later, still complaining of persistent headache and weakness.

From that time until his admission to the Hospital of the University of Pennsylvania the patient rested a great deal because weakness and headaches continued. On Dec. 6, 1932, he again was found on the floor moaning, and shortly thereafter there was another attack of projectile vomiting. At this time he was not stuporous or disoriented; he complained of severe headache with a feeling of "electricity in his legs" and stated that this attack was preceded by a sudden sharp pain in the head

7. Woltman, H. W., and Shelden, W. D.: Neurologic Complications Associated with Congenital Stenosis of the Isthmus of the Aorta, Arch. Neurol. & Psychiat. **17**:303, 1927.

which was so severe that he felt unable to answer when he was called. A few hours later he became stuporous. The previous medical history was irrelevant except for the fact that at the age of 10 years he was knocked unconscious by being struck on the head by a falling beam.

Examination.—At the time of admission the significant findings on physical examination were: The patient lay in bed in a stuporous condition. He could be aroused with difficulty. Speech was mumbling, thick and indistinct. Under persuasion he was able to recognize objects, but when left to himself he quickly

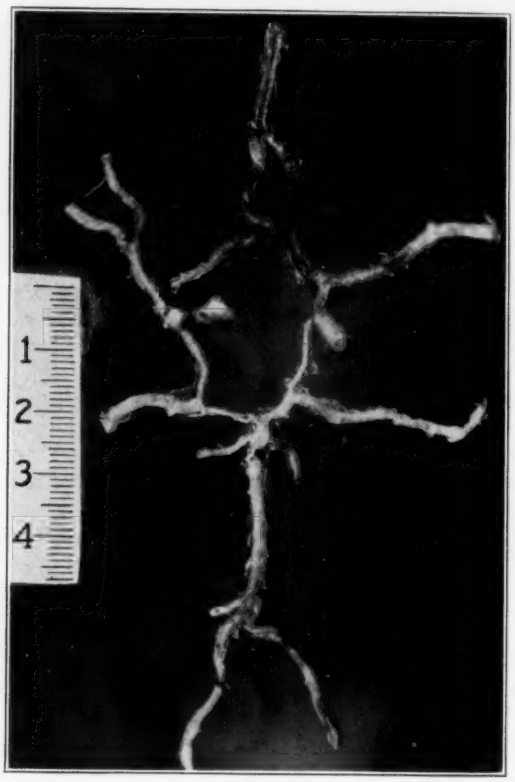

Fig. 1.—Dissection of the circle of Willis, showing a ruptured aneurysm at the junction of the right anterior communicating and the anterior cerebral artery.

became stuporous. The neck was markedly rigid. There was no focal weakness of any of the extremities. All of the deep and superficial reflexes were equal and markedly exaggerated. A bilateral Kernig sign and a bilateral Babinski sign were elicited.

A tentative diagnosis of recurrent spontaneous subarachnoid hemorrhage was made.

Lumbar puncture revealed frankly hemorrhagic fluid. The initial pressure was 210 mm. of water. Microscopic study of the spinal fluid revealed 165 leukocytes and 133,000 erythrocytes per cubic millimeter. The fluid contained no organisms on smear and was sterile on culture. A second lumbar puncture was done on

December 9, with essentially the same findings. On the following day the intraspinal pressure was normal and no fluid was withdrawn. Roentgen examination of the head by Dr. Pendergrass showed no evidence of fracture of the vault or the posterior fossa. The pituitary fossa was normal in size; the left side of the dorsum sellae was normal, but the right side showed an unusual appearance which might have been due to a parasellar lesion. The Wassermann test of the blood was negative. The blood pressure was 125 systolic and 85 diastolic. Repeated blood counts revealed neutrophilic leukocytosis but nothing else of significance.

Neurologic examination by Dr. M. J. Cooper confirmed the neurologic findings already described.

Examination of the eyes by Dr. A. G. Fewell gave negative results. The pupils were equal and reacted promptly to light and in accommodation. The extra-ocular muscles and the fundi were normal. The condition of the patient did not permit

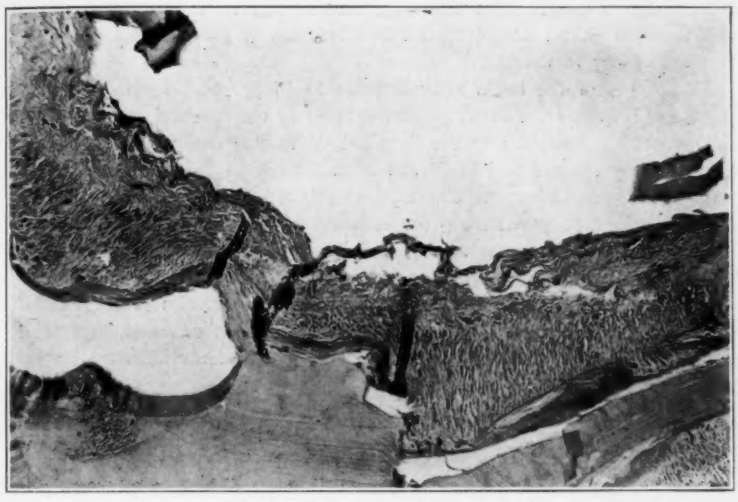

Fig. 2.—A section through the part of the wall of a small cerebral artery opposite the main limb of a bifurcation. It will be observed that there is a defect in the musculature in the region of the small folds in the section. Magnification, × 92.

a careful examination of the visual fields with the perimeter, but no hemianopia was detected by means of the feeding test.

The temperature on admission was subnormal, probably as a result of shock. Subsequently, it climbed perpendicularly without diurnal variation, reaching a peak of 108.6 F. at the time of death on Dec. 12, 1932, five days after admission.

Autopsy.—All of the internal organs were normal except the lungs, which showed confluent lobular pneumonia, and the brain, which revealed subarachnoid hemorrhage and a ruptured aneurysm of the right anterior communicating artery.

Dr. Parson's report on the brain was as follows: "The skull is thin. The dura is of the usual thickness and texture. The leptomeninges over the cerebral hemispheres are thin and transparent. The cisternae contain bloody fluid. Over the base of the frontal lobes, in the longitudinal fissure and over the interpeduncular space and the base of the temporal lobes, there is an extensive recent subarachnoid

hemorrhage. This hemorrhage is most extensive anterior to the optic chiasm. When the clotted blood was cleared away from the arteries at the base of the brain a saccular aneurysm 3 by 2 by 2 mm. was found at the acute angle of the junction of the anterior cerebral and anterior communicating arteries. This aneurysm is seen to have ruptured, the more distal half having been separated at about the equator and being attached to the proximal half by a narrow strip. This aneurysm lies close to the arteries, and its lumen communicates with the arteries by an orifice about 0.75 mm. in diameter. The proximal half of the aneurysm has a thin wall and a smooth intima. The distal half has a thicker, more rigid wall, and there is a thin thrombus over its inner surface. The other arteries at the base of the brain show no gross abnormality.

"The brain substance is of the usual texture and configuration. No areas of softening or discoloration are seen.

"The hypophysis and its stalk are of the usual size and shape. The left posterior clinoid process is considerably shorter than the right. The pituitary fossa is of normal size and shape, except for slight distortion of the posterosuperior margin, which slants away to the left.

"Examination of the brain after fixation in 10 per cent formaldehyde showed that dense adhesions exist between all the lobes of the cerebral hemispheres. After separation of the adhesions in the longitudinal fissure extensive hemorrhage was found, extending upward and backward from the site of the aneurysm and spreading over the corpus callosum. Cut sections of the brain reveal normal tissue with no hemorrhage or other visible gross lesions.

"Numerous sections from the cerebral hemispheres and the brain stem reveal extensive subarachnoid hemorrhage with no significant lesion of the nerve tissue. Sections through the bifurcation of the medium-sized arteries reveal the anomaly of the musculature described by Wiley Forbus. This consists of a defect in the development of the muscular layer at the acute angle of the bifurcation, the other coats being intact."

SUMMARY

Since the time of Sir William Gull, it has been surmised that otherwise unexplained subarachnoid hemorrhage in young persons might result from ruptured intracranial aneurysms.

The pathologic studies of intracranial aneurysms made by Forbus have given a rational explanation of the reasons for their formation and for their development at the usual sites.

The clinical picture, portrayed by Albright, of cases in which there is an aneurysm at or near the junction of the internal carotid artery and the circle of Willis is so distinctive that the diagnosis should be made ante mortem.

Intracranial aneurysms originating at a point in the circle of Willis, where focal signs are not produced, cannot be accurately diagnosed. Their presence can only be surmised in case of the occurrence of spontaneous subarachnoid hemorrhage in young persons.

Ligation of the common carotid artery on the side of the lesion seems to be the therapeutic measure of choice, despite the danger of hemiplegia from occlusion of the internal carotid artery.

2025 Spruce Street.

DIAGNOSTIC VALUE OF MYELOGRAPHIC STUDIES OF THE CAUDAL DURAL SAC

H. C. Coggeshall, M.D., and T. J. C. von Storch, M.D., Boston

Roentgenologic vizualization of the caudal portion of the spinal dural sac offers a means to detect deformities of its contour which may be produced by neoplasms, congenital abnormalities or traumatic lesions. Visualization of the caudal sac has been produced by intrathecal injections of substances opaque to the x-rays, namely, halogen oils. The chief disadvantages in the use of these substances are: First, irritation is produced by a foreign body in the subarchnoid space; second, the absorption of the oil is very slow (it may never be completely absorbed), and third, owing to the viscosity of the oils used false defects often cause confusion in interpretation. The use of halogen oils is not without risk or limitations, and for this reason we propose the intrathecal injection of air or oxygen. Air was first used to visualize the brain and its ventricles and has not to our knowledge been used as herein described. It was, however, suggested in this connection by Dandy.[1]

METHOD

The patient is placed on an elevating x-ray table (gastro-intestinal or cystoscopic). With the table horizontal, lumbar puncture is performed, 2 per cent procaine hydrochloride being used as a local anesthetic. The lumbar needle is provided with a manometer to measure the spinal fluid pressure at different intervals during the procedure. The initial spinal fluid pressure is determined; then the table is elevated until the patient's head is 30 degrees below the horizontal plane. This causes the injected air to collect in the tip of the caudal sac rather than rostrally. Next, a 20 cc. syringe is attached to the needle and 10 cc. of cerebrospinal fluid is slowly aspirated, after which 5 cc. of air is slowly injected with the same syringe. Then 10 cc. of fluid is withdrawn, followed by the injection of 10 cc. of air; this process is continued until the caudal sac is emptied of fluid. When the process is complete there is 5 cc. less air than the amount of cerebrospinal fluid that has been removed. This allows for expansion of the injected air as it warms to body temperature. The needle is removed, and two sets of anteroposterior stereoscopic x-ray exposures are taken over the first sacral vertebra.

The only precaution that need be observed following the injection is to keep the head low. There is no serious complication except severe headache. If the head is elevated the air shifts upward to the brain and immediately causes headache. This may be avoided by keeping the head lower than the sacrum for a period of twelve hours.

COMMENT

By the method described, the lower part of the dural sac has been studied in three normal persons. The roentgenogram shows a black column of air that fills the entire lower tip of the caudal sac. Along the lateral wall are small projections of the air column which indicate the extension of the air column to surround the roots of the spinal nerves. Stereoscopic visualization causes the sac to stand out as a hollow cone.

From the Neurological Unit of the Boston City Hospital.

1. Dandy, W. E.: Ventriculography, Ann. Surg. **68**:5, 1918.

The outline of the dural sac may be brought into relief by two methods: first, by filling the subarachnoid space with a radiopaque substance and, second, by using a substance that is less opaque to the x-rays than the wall of the sac. Halogen oils are used in the former method and gases in the latter. The halogen oils are used to the greatest advantage to demonstrate a block in the spinal canal caused by adhesions of the meninges or by a tumor. In the caudal sac, lying below the tip of the spinal cord, the halogen oil forms a mass that can be examined roentgenologically only in one plane. The chief advantages in using air are: (1) the stereoscopic visualization of the dural sac, (2) the absorbability of air

Roentgenogram of the caudal sac.

and (3) its failure to adhere to the caudal filaments as the oils often do, thus confusing the normal with the pathologic.

The spinal dura mater may be considered as a cylindric tube terminating with a conical end at the level of the second sacral vertebra. It is loosely suspended in the vertebral canal and is anchored above to the periosteum of the foramen magnum and below to the periosteum of the sacrum by the filum terminale externum. The spinal dural sac is separated from the walls of the vertebral canal by the cavum epidurale, which is occupied by fat, a plexus of thin-walled veins and the roots of the spinal nerves. Any expanding lesion or mass, either of the dural sac or external to it, produces distortion of the wall of this sac. A mass in the dural sac will be outlined by the air in the sac.

SUMMARY

Myelography offers a simple, safe and easy diagnostic procedure for visualizing deformities of the caudal dural sac. The common causes of deformity are neoplasms, congenital defects and traumatic deformities.

We offer this note without the presentation of cases with proved pathologic changes in the hope that others will find the method a useful procedure. An accurate evaluation of the procedure will be postponed until a sufficiently large series of cases has accumulated.

NOTE.—Since forwarding this manuscript for publication, we have discovered that Dr. Dandy has utilized in his clinic a form of the method described, as suggested by him in 1918. Priority belongs to Dr. Dandy. However, we feel that, as this is unpublished, the method should be called to the attention of the medical profession in general. The method as described deals solely with myelography caudal to the insertion of the lumbar puncture needle.

REENFORCEMENT OF THE KNEE JERK IN CHILDREN

FRANK E. STEVENSON, M.D., CINCINNATI

There is considerable normal individual variation in the degree of the flexion angle of the knee at which the patellar reflex is most readily elicited. With the patient in the dorsal position, the angle at which the optimum response is obtained can usually be found by slowly and rhythmically tapping the patellar ligament while the previously extended leg is passively and slowly flexed.

Often it is necessary to reenforce the knee jerk in order to determine whether the reflex is absent or hypo-active. The more commonly employed methods of reenforcement frequently are too difficult for the young child to comprehend. Then, too, the physician often finds it cumbersome to determine whether or not the reenforcement is being consistently performed and at the same time to observe the quadriceps response.

The knee jerk can often be reenforced by active plantar flexion of the foot and toes. The physician can usually obtain this by instructing the patient to turn or bend the toes downward and, immediately following this command, passing the palm of his hand downward over the dorsum of the foot and outward over the ends of the toes. Then, while reminding the patient at frequent and regular intervals to keep the toes turned downward, he elicits the knee jerk in the manner previously described. Occasionally the reflex is obtained only when the patellar tendon is tapped synchronously with plantar flexion of the foot and toes. Sometimes, too, better results are obtained when both feet take part in the reenforcement.

From the Department of Pediatrics, College of Medicine, University of Cincinnati, and the Children's Hospital.

SPECIAL ARTICLES

THE NARCOLEPSIES

CRYPTOGENIC AND SYMPTOMATIC TYPES

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The problems of narcolepsy are still matters of controversy. Gélineau,[1] in 1880, and Redlich [2] and Adie,[3] in 1926, thought that they were dealing with a disease entity, with a disease per se. Gélineau [1] made a significant statement when he published his famous case, starting his paper with the now historic and much quoted phrase: "I propose to give the name of narcolepsy (somnolence and to seize) to a rare neurosis, or one little known up to the present time, characterized by an imperious desire to sleep, sudden and of short duration, reproducing itself at intervals more or less closely related." This name has been accepted by various workers, with the result that all kinds of clinical manifestations appeared under Gélineau's *nomen morbi*. In 1902, Löwenfeld [4] objected to the loose application of the term narcolepsy and insisted that the term should refer to cases characterized not only by short attacks of sleep but also by attacks of loss of muscular tonus. In 1917, Singer [5] suggested the name "hypnolepsy" for this group and excluded spasmophilic attacks with lethargy, hysterical sleepy states, petit mal epileptic states and other states. He believed that hypnolepsy is a definite neurosis and is due to a degenerating constitutional foundation.

Read at the Fifty-Ninth Annual Meeting of the American Neurological Association, Washington, D. C., May 11, 1933.

1. Gélineau: De la narcolepsie, Gaz. d. hôp. **53**:626, 1880.

2. Redlich, E.: (*a*) Zur Narkolepsiefrage, Monatschr. f. Psychiat. u. Neurol. **37**:85, 1915; (*b*) Ein weiterer Beitrag zur Narkolepsiefrage, Jahrb. f. Psychiat. u. Neurol **37**:68, 1917; (*c*) Ueber Narkolepsie, Ztschr. f. d. ges. Neurol. u. Psychiat. **95**:256, 1925.

3. Adie, W. J.: Idiopathic Narcolepsy: A Disease Sui Generis with Remarks on the Mechanism of Sleep, Brain **49**:257, 1926.

4. Löwenfeld, L.: Ueber Narkolepsie, München. med. Wchnschr. **49**:1041, 1902.

5. Singer, K.: Echte und Pseudo-Narkolepsie (Hypnolepsie), Ztschr. f. d. ges. Neurol. u. Psychiat. **36**:278, 1917.

Wenderowič,[6] in 1924, accepted Singer's point of view. He thought that the term narcolepsy had attained too wide a significance and was being used to designate all types of hypnoid states. He proposed to use Singer's term hypnolepsy as a general term for the "disease in general," and suggested the following classification: (1) genuine hypnolepsy (Gélineau's disease); (2) symptomatic hypnolepsy (probably a post-encephalitic syndrome); (3) narcolepsy (symptomatic hypnoid states of previously noted disease). He thought, with many other authors, that the so-called genuine hypnolepsy was a rather rare disorder and suggested that Henneberg's[7] nomenclature of the *kataplektische Hemmung* be modified to *Kataplexie* for the attacks characterized by the affective loss of tonus. Jelliffe[8] was among the earliest to emphasize the fallacy of the nosologic classifications in general and to point out that narcolepsy is not a "disease" per se or a *morbus sui generis*, as Gélineau called it, but is a symptom that may occur in a variety of conditions. Wilson[9] and Lhermitte and Tournay[10] have expressed the same opinion in recent years. The narcoleptic symptom complex may be seen in its entirety or in part in a variety of conditions. The attacks have been observed in cases of chronic epidemic encephalitis, multiple sclerosis (Jakobsohn[11]), polycythaemia rubra (Lhermitte and Peyre[12]), trauma to the head (Souques[13]), cerebral concussion (Lhermitte[14]), cerebral neoplasms, cerebral arteriosclerosis and other conditions. There are, however, cases in which a most careful examination fails to reveal any definite evidence of involvement of the central nervous system or of any other system of the organism. These cases lend themselves, according to our opinion (Jelliffe), to psychodynamic interpretations, and such attacks may be looked on as an expression of psychologic regressive mechanisms.[8]

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6. Wenderowič, E.: Hypnolepsie (Narcolepsia Gélineau) und ihre Behandlung, Arch. f. Psychiat. **72**:459, 1924.

7. Henneberg, R.: Ueber genuine Narkolepsie, Deutsche med. Wchnschr. **41**: 1585, 1915.

8. Jelliffe, S. E.: Narcolepsy: Hypnolepsy; Pyknolepsy, M. J. & Rec. **129**: 269 and 313, 1929.

9. Wilson, S. A. K.: The Narcolepsies, Brain **51**:63, 1928.

10. Lhermitte, J., and Tournay, A.: Rapport sur le sommeil normal et pathologique, Rev. neurol. **1**:751, 1927.

11. Jakobsohn, E.: Ueber Narkolepsie, Zentrabl. f. Neurol. u. Psychiat. **45**: 284, 1927.

12. Lhermitte, J., and Peyre, E.: La narcolepsie-cataplexie, symptôme révélateur et unique de l'érythrémie occulte: Maladie de Vaquez, Rev. neurol. **1**: 286, 1930.

13. Souques, A.: Narcolepsie d'origine traumatique; Ses rapports avec une lésion de la région infundibulo-hypophysaire, Nev. neurol. **25**:521, 1918.

14. Lhermitte, J.: La forme narcoleptique tardive de la commotion cérébrale, Paris méd. **8**:509, 1918.

The paroxysmal nature of the attacks, the occurrence of aura in certain cases, the peculiar confusional states observed in some instances after the attacks, the epileptic heredity reported in some cases and the combination of both epileptic and narcoleptic attacks in some instances raise the question whether this is not a condition related to the epilepsies and whether it would not be wiser to bring the narcolepsies and the epilepsies under one grouping. This position was considered by Kraepelin,[15] and more recently has been discussed by Serejski and Frumkin.[16]

In order to throw some light on the whole set of problems we have made an attempt to investigate as many cases of attacks of sleep reported in the literature as possible. We have gone as far back as Fournier [17] in 1813. A more detailed historical review was given by one of us [10] a few years ago (Jelliffe [8]). A study of the casuistic material suggested a certain classification of the cases.

In one group we have listed the cases of hypersomnia and those of attacks of sleep in persons with a definite psychopathologic background. These cases may not properly belong to the narcolepsies. In some instances the attacks of sleep lasted for hours and days. Here belong the cases of "somnosy" of Gowers. The earliest cases in the literature were reported by Fournier,[17] in 1813, in the "Dictionnaire des sciences" under the title "Cas rares." A most recent report is that by Claude and Baruk [18] in 1928. Altogether there are 27 publications with a total of 64 cases reported up to 1931. Some of the cases belong definitely to the group of psychoneuroses; others, to schizophrenia or manic-depressive psychoses. Most interesting among them are the cases of Dana,[19] published in 1884, the case of the "sleeping Effie" reported by Edwards [20] in 1848 and the case of "La dormeuse d'Oknö" published by Fröderström [21] in 1912.

In a second group we have segregated cases in which there is definite evidence of cerebral involvement and those in which there are irre-

15. Kraepelin, Emil: Psychiatrie, ed. 8, Leipzig, Johann Ambrosius Barth, 1913.

16. Serejski, M., and Frumkin, Y.: Narkolepsie und Epilepsie, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:233, 1930.

17. Fournier: Cas rares, Dictionnaire des sciences médicales, Paris, Crapart & Panckoucke, 1813, vol. 4, p. 204.

18. Claude, H., and Baruk, H.: Les crises de catalepsie: Leur diagnostic avec le sommeil pathologique; Leurs rapports avec l'hystérie et la catatonie, l'Encéphale **23**:373, 1928.

19. Dana, C. L.: On Morbid Drowsiness, J. Nerv. & Ment. Dis. **11**:153, 1884.

20. Edwards, J.: Report of a Remarkable Case of Somnolence, Lancet **1**: 309, 1848.

21. Fröderström, H.: La dormeuse d'Oknö, N. icnog. de la Salpêtrière **25**: 267, 1912.

versible somatic pathologic changes. The earliest case of this group is that of Paz,[22] reported in 1876. Of particular interest are the cases of Dana,[23] reported in 1916, and those of Fulton and Bailey,[24] published in 1929. There are 88 cases of this type reported in thirty-three communications.

A third group comprises cases of chronic epidemic encephalitis with attacks of sleep alone or with both attacks of sleep and cataplectic attacks. The first case we have noted is that of Kraus,[25] reported in 1921. Up to 1931, 29 cases were reported in 22 publications. The largest number of cases were given by Spiller,[26] in 1926, and by Stransky,[27] in 1929.

In a fourth group we have assembled cases in which a combination of both narcoleptic and epileptic attacks are described. The first case found is that of Siemens,[28] in 1879, and the more recent one is that by Thomas,[29] in 1928. Up to 1931, 30 cases had been reported in 10 communications.

Finally there is a fifth group—cases we should like to designate as the cryptogenic type on account of lack of any definite signs of pathologic change. The first clearcut cases were those of Thümen[30] and Fricker,[31] reported independently in 1841, long before the word narcolepsy was coined by Gélineau. Ten years later, Caffé[32] published his case. This is the case that Gélineau himself reported. Altogether, up to 1931 there had been 270 cases reported in 141 communications. These figures are much greater than those given by previous investigators and should help to dispel the notion of the rarity of the disorder.

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22. Paz, E.: Mal de sueño, Crón. méd.-quir. de la Habana **2**:328, 1876.

23. Dana, C. L.: Morbid Somnolence and Its Relation to Morbid Endocrine Glands, M. Rec. **1**:89, 1916.

24. Fulton, J. F., and Bailey, P.: Tumors in the Region of the Third Ventricle: Their Diagnosis and Relation to Pathological Sleep, J. Nerv. & Ment. Dis. **69**:1, 1929.

25. Kraus, W. M.: Encephalitis with Recurrent Narcolepsy, J. Nerv. & Ment. Dis. **53**:126, 1921.

26. Spiller, W. G.: Narcolepsy Occasionally a Postencephalitic Syndrome, J. A. M. A. **86**:673 (March 6) 1926.

27. Stransky, E.: Zum Problem und zur Klinik der Schlaf- und Tonusverlustanfälle, Wien. klin. Wchnschr. **42**:612, 1929.

28. Siemens: Zur Lehre vom epileptischen Schlaf und Schlaf überhaupt, Arch. f. Psychiat. **9**:72, 1879.

29. Thomas, André: A propos d'un cas de narcolepsie, Presse méd. **36**:1273, 1928.

30. Thümen: Ein Fall von Schlafsucht, Med. Ztg. **49**: 1841; Lanstaat Ber. **2**: 175, 1841.

31. Fricker: Ein Fall von Schlafsucht, Med. Cor.-Bl. Würst. ärztl. Verhandl. **11**:213, 1841.

32. Caffé: Maladie du sommeil, J. d. conn. méd. prat. **39**:323, 1862.

THE SYMPTOM COMPLEX OF THE NARCOLEPSIES

There is still considerable confusion as to what constitutes the symptomatology of narcolepsy. Some investigators emphasize only the attacks of sleep; others stress the attacks of loss of tonus, and finally there is a third group of workers who believe that both types of attacks are essential to complete the picture of the so-called true narcolepsy. We may say here that from our experience only in the cryptogenic group are both types of attacks described, while in the symptomatic variety one sees more often one or the other type of seizure.

The attacks of sleep may occur at any time of the day and under all kinds of circumstances, while speaking, eating or walking. Chavigny's [33] patient fell asleep while riding a bicycle. One of Jelliffe's [8] patients would find herself in a ditch while driving a car. B. Fischer [34] reported a case with attacks intra coitum. Attacks have been observed in women during the menstrual period (Ballet,[35] Fischer [34] and Kahler [36]). The attacks usually last from a few minutes to half an hour. During the attacks of sleep there is a decrease in the tonus of the muscles; on a few occasions an increase of tonus was observed. As a rule the pulse is slowed; occasionally it may become tachycardiac. Some of the patients dream during the attacks; others have hypnagogic hallucinations.

Usually the sleep is not very sound, and some of the patients are easily awakened from the attack. Some are able to perceive acoustic impressions very vaguely during these states; they are able to hear what is said but are unable to answer (Westphal,[37] Goldflam [38] and Fischer [34]). The onset of an individual attack is rapid—*schlagartig* as the Germans describe them.

According to Goldflam,[38] the pupils are contracted during the attacks as in sleep myosis. Gélineau,[1] on the other hand, stated that in his observations the pupils were dilated during the seizures and contracted on awakening. Curschmann and Prange [39] obtained good pupillary reactions during the attacks.

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33. Chavigny, M.: Narcolepsie (sommeil pathologique), Lyon méd. **103**:1073, 1904.

34. Fischer, B.: Zur Frage der Narkolepsie, Ztschr. f. d. ges. Neurol. u. Psychiat. **90**:599, 1924.

35. Ballet, G.: Contribution à l'étude du sommeil léthargique (quelques cas de narcolepsie) Rev. méd., Paris **2**:945, 1882.

36. Kahler, H.: Zur Kenntnis der Narkolepsie, Jahrb. f. Psychiat. u. Neurol. **41**:1, 1922.

37. Westphal, C.: Eigentümliche mit Einschlafen verbundene Anfälle, Arch. f. Psychiat. **7**:631, 1877.

38. Goldflam, S.: Zur Frage der genuinen Narkolepsie und ähnlicher Zustände, Deutsche Ztschr. f. Nervenh. **82**:20, 1924.

39. Curschmann, H., and Prange, F.: Ueber Einschlafsucht (Narkolepsie und Verwandtes), Deutsche Ztschr. f. Nervenh. **86**:97, 1925.

The nightly sleep of these persons is usually disturbed. Somnambulistic wanderings have been reported. The awakening is usually rapid, but in some instances confusional states or sleep drunkenness was observed.

Other important symptoms are the attacks of loss of muscular tonus produced by emotional states, especially by hearty laughter and occasionally by anger or other unpleasant affects. These attacks are produced not only by an active affect but sometimes, as in Somer's [40] case, by a recollection or by a vivid representation of an affect which previously has produced an attack. In the cases of Gélineau,[1] Kahler [36] and B. Fischer [34] a very pronounced affect or, better, a stimulus heavily charged with affect produced at one time cataplectic attacks and at other times attacks of sleep. There are also cases in which spontaneous attacks occurred without stimuli. This is an important point which will be discussed later in a consideration of the pathogenesis and of the relationship of the narcolepsies to the epilepsies.

The attacks may last for a few minutes only, and consciousness is impaired to some extent. Rudimentary attacks are also described when the patient's knees or head bends for a second or so. During the fully developed attacks the patients are unable to move their limbs and remain speechless. Gélineau [1] gave the name "chute" or "astasia" to these attacks. Löwenfeld [4] named them *kataplektische Starre*—inability to maintain the erect posture of the body. Henneberg [7] spoke of *kataplektische Hemmung;* Redlich [2] used the term *affektiver Tonusverlust;* Trömner, [41] *Affektatonie;* Weech,[42] *emotionelle Asthenie* and Rosenthal,[43] *affektive Adynamie.* Occasionally there are urinary incontinence, peculiar paresthesias and, at times, respiratory difficulties. During the cataplectic attacks the corneal and patellar reflexes are absent (Wilson [9]). Wilson also elicited dorsal extension of the big toe on plantar stimulation. Mankowsky [44] found that the patellar and achilles reflexes are absent during the attacks; the pupils, however, seem to show a normal reaction to light. A rise in temperature during these seizures has been reported.

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40. Somer, W.: Zur Narkolepsiefrage, Wien. klin. Wchnschr. **34**:132, 1921.

41. Trömner, E.: Das Problem des Schlafes, Munich, J. F. Bergmann, 1912.

42. Weech, A. A.: Narcolepsy—A Symptom Complex, Am. J. Dis. Child. **32**: 672 (Nov.) 1926.

43. Rosenthal, C.: Ueber die krankhaften Dissoziationszustände bei der echten Narkolepsie und dem verzögerten psychomotorischen Erwachen (Wachanfälle), Arch. f. Psychiat. **84**:120, 1928.

44. Mankowsky, B.: Zur Pathologie kataplegischer Anfälle bei Narkolepsie (auf Grund eines Falles von Encephalitis), Arch. f. Psychiat. **61**:340, 1926.

PERSONAL OBSERVATIONS

Our material consists of a number of cases which were observed at the Neurological Clinic of the New York Post-Graduate Medical School and Hospital, at Manhattan State Hospital, at the Vanderbilt Clinic (courtesy of Dr. Louis Casamajor) and in private practice. Among our cases there are patients with narcoleptic attacks without any definite etiology; others presented a history of encephalitis or evidence of involvement of the central nervous system and the endocrine apparatus. A few may be picked out for illustrative purposes.

CRYPTOGENIC ATTACKS OF NARCOLEPSY

CASE 1.—Dorothy T., a woman, aged 21, born in the United States, an art student, whose family history was without significance and whose early personal history was uneventful, had been in perfect health until the age of 19, when there developed a strong inclination to sleep, which would come on twice or three times a day. She would fall over her charcoal while drawing. The same would occur in the subway, during lectures, in movies and in other situations. The desire to sleep set in suddenly; the patient was unable to overcome it. She would sleep for only a few minutes and wake up. Sometimes she could hear people about her talking; "it seems as if only a part of me is asleep," is the way she expressed it.

A year later, at any time she happened to laugh she would become so weak that she had to hold on to something to keep from falling. She also noted that while laughing or when she was tired her eyes were apt "to go cross-eyed." She then saw double for some seconds until she got her eyes straight by moving them up and down. On account of this condition she came to the Vanderbilt Clinic on Dec. 20, 1927. Physical examination revealed nothing of importance, except perhaps somewhat increased patellar reflexes. There were no signs of involvement of the central nervous system or of any somatic illness The patient failed to report to the clinic. She did, however, send a letter four months later stating that she was feeling better; she did not, however, mention the attacks of weakness, saying only: "the sleeping in the day time has become a habit."

CASE 2.—Anna G., a white married woman, aged 40, born in the United States, who was without hereditary taints and had had no serious illnesses, came to the Vanderbilt Clinic on Oct. 26, 1927, complaining that a year previously she noted that while "laughing at a story or anything of that nature," she would become "all numb" and would sink down slowly without actually falling. At about the same time a habit of dropping to sleep for a few minutes at almost any time of the day developed. She had noticed several times that she would do things without being aware of the action, such as mixing sugar and flour while cooking. While sleeping she answered questions of which she had no recollection afterward. Physically, she was well developed; she showed only a few neurologic signs, such as slight irregularity and inequality of pupils. She reported once, but as she could not be located after this further study was impossible.

CASE 3.—*History* (as reported by Dr. Levine and from the notes of Dr. Jelliffe [8]). —V. B., a girl, aged 19, with no occupation, was admitted to the medical service of the Johns Hopkins Hospital on Jan. 14, 1927, complaining of attacks of falling when she laughed or was frightened, attacks of drowsiness and peculiar attacks of

amnesia. Cataplectic symptoms had begun at the age of 14. When she laughed heartily or was frightened she became weak and dizzy and fell to the ground. These attacks were never followed by sleep. Attacks of sleep began two years later. She often fell asleep at the theater or while motoring. She slept for from five to fifteen minutes and was then wide awake. The onset and the frequency of the attacks of amnesia were not stated. Once when riding with her mother and friends in an automobile, the friends were put off at a certain street and she and her mother proceeded home. After they returned to the house she was unable to remember anything that had happened after she had entered the car. During the attack, the mother and friends had noticed nothing unusual in her appearance or behavior.

At the age of 2 weeks she had had an attack of "convulsions," lasting for two minutes, about which nothing is known. There were no further convulsions. She began to menstruate at 13; the periods were always regular.

Physical Examination.—The patient's height was 61½ inches (156.27 cm.); her weight was 111 pounds (50.31 Kg.). The thyroid isthmus was a little full and smooth; no nodules were felt. The eyes were a little prominent, and the lid slits rather wide. The pulse rate was 76. The distribution of hair was normal. The pupils were large and reacted normally. Examination otherwise gave negative results. The blood pressure was 110 systolic and 75 diastolic.

Laboratory Examinations.—The urine was normal; the daily output varied from 1,000 to 2,300 cc. The hemoglobin content was 86 per cent; the red cell, white cell and differential counts were normal. The Wassermann reaction of the blood was negative. The blood sugar was 78 mg. per hundred cubic centimeters; uric acid, 4.2 mg. The spinal fluid contained 4 cells; the Wassermann reaction was negative; the colloidal gold curve was negative; the spinal fluid sugar was 69 mg. per hundred cubic centimeters.

Ophthalmologic Examination.—Moderate compound hyperopic astigmatism was observed.

Course.—While under observation the patient at no time had fever. She had two or three attacks of sleep daily.

Comment.—The unusual feature in this case was the occurrence of attacks of amnesia. Further details of the case showed that the patient had pyknoleptic, narcoleptic, *Lachschlag* and epileptic attacks.

NARCOLEPTIC ATTACKS WITH POSSIBLE ENDOCRINE INVOLVEMENT AND ENCEPHALITIS

Case 4.—Bessie F., a girl, aged 18, born in the United States, a stenographer, whose early development had been uneventful, and who descended from healthy stock without any evidence of hereditary taints in ascendants or collaterals, had always enjoyed good health except for an attack of "flu" at the age of 15. At 16 a definite change in personality was noted by members of the family. She became cranky, impatient and easily annoyed. She also gained 25 pounds (11.3 Kg.) in one year. Since the age of 17, a certain loss of control of the muscles of the face had been manifest. She also became drowsy and would fall sound asleep in the daytime if left alone. She would fall asleep in trains and the subway on the way to work and would lie down to sleep immediately on reaching home. Before the onset of this condition the menstrual periods had been regular and the flow of normal amount, but since the onset they had become irregular and profuse. During

the last year she noted a tendency to "keel over" while laughing. At about the same time she began to perspire profusely and to have difficulty in breathing; her mouth became unusually dry and her appetite ravenous. There were no complaints of visual disturbances, such as diplopia. She came to the Vanderbilt Clinic in November, 1927.

Examination.—The patient was in a good state of nutrition, weighing 140 pounds (63.5 Kg.), and showed no neurologic signs. Laboratory examination of the blood revealed: red cells, 4,096,000; white cells, 12,000, with neutrophils, 52 per cent; eosinophils, 1; small lymphocytes, 38; large lymphocytes, 4; transitional cells, 5. The basal metabolic rate was 15 below the average normal. Stereoscopic examination of the skull revealed an unusually small sella turcica, measuring about 8 by 4 mm.; there was also a definite bridging of the clinoid processes, which appeared to inclose completely the pituitary fossa. Other laboratory examinations, including that of the gastro-intestinal tract, gave normal results. There was no evidence of polydipsia or polyuria.

Comment.—It is interesting that during the basal metabolic procedure the patient fell asleep. She would also fall asleep every time she came for treatment, which consisted of hypodermic injections of epinephrine. She would wake up during the insertion of the needle, but would immediately fall asleep again after having the medication; the sleep would last for half an hour.

Unfortunately this patient left New York and her whereabouts are unknown, so that a further follow-up is impossible.

NARCOLEPTIC ATTACKS ON A POSSIBLE ENDOCRINE BASIS

Case 5.—Joseph D., a boy, aged 15, born in the United States of Hungarian parents, whose father was stout and tall, and died of pulmonary tuberculosis, at birth weighed 11 pounds (5 Kg.). He began to walk at the age of 16 months and to talk at 2 years. He was rather retarded at school and on three occasions failed to secure promotion. He had measles at the age of 2 and chickenpox when 5. At about the age of 14, he began to fall asleep in school, at home and sometimes on subway platforms. The attacks of sleep would last for only a few minutes. They overtook him particularly when reading or writing. During the attacks he looked like a child naturally asleep; he awoke spontaneously and was also easily awakened. Occasionally, on the average of once in three months, he had peculiar feelings in the head, lasting only a moment, which he called "electric shocks." He gained 43 pounds (19.5 Kg.) in one year.

He was brought to the Neurological Clinic of the New York Post-Graduate Medical School and Hospital on Jan. 30, 1929.

Examination.—The patient, a rather overfed boy, weighed 157 pounds (72.1 Kg.). His height was 168 cm. The body contour and distribution of hair were of the feminine type. The breasts were large; the abdomen was pendulous and obese. The thyroid gland was slightly palpable. The palpebral fissures were unequal; on the right there was esotropia, but no diplopia. The triceps and patellar reflexes were exaggerated; bilaterally there was an equivocal Babinski sign, without confirmatory signs. The pulse rate in the lying position was 120; the blood pressure was 130 systolic and 70 diastolic; there were no cardiac murmurs. The nails were cyanotic; the skin was dry and of coarse texture. Examination of the blood showed: red cells, 3,840,000; hemoglobin, 65 per cent; polymorphonuclear cells, 54 per cent; mononuclears, 5; small lymphocytes, 25; large lymphocytes, 15. The urine was normal, except for an occasional white blood cell. The spinal fluid was

clear, and gave negative results for globulin and cells. The Wassermann reaction of the blood serum and of the spinal fluid was negative. The colloidal gold curve was normal. The basal metabolic rate was 3 per cent below the average normal. The sella turcica was a shade smaller than average, with a sharp contour and no evidence of erosion or necrosis. A sugar tolerance test gave normal results.

Course.—The patient failed to report to the clinic, and an effort at a follow-up study was unsuccessful.

NARCOLEPTIC SEIZURES IN CHRONIC EPIDEMIC ENCEPHALITIS

Case 6 (a preliminary report was made by Dr. Bromberg).—Frank H., aged 46, a gardener, born in Austria, who had been in the United States since 1903, had had an uneventful infancy and childhood. He received a public school education in Austria, and later worked as a farmer and gardener. He married when young, but his wife had no children. He was amiable and congenial, except that occasionally he would have fits of temper. At such periods he used profane language and would keep away from other people for two or three days. In March, 1920, he became suddenly ill with headache, diplopia, fever and somnolence. He was treated in a city hospital for about two weeks and apparently improved a great deal. He went home, resumed his usual occupation and seemed to get along fairly well. However, since his return from the hospital he would often become sleepy and would tire easily, and after a while he was unable to work for more than half a day.

In 1921 he began to fall asleep while talking or eating. He would sleep for from five to fifteen minutes and awake spontaneously, quite refreshed. He could also be aroused by mild shaking. The attacks occurred about once a day. About eight months after the onset of the attacks of sleep he noticed that "when he became aggravated or surprised" he would fall to the ground in a heap. Later, laughter would cause similar attacks. In 1923 he could no longer work and was taken to a hospital on March 23, 1923. Physical examination at that time revealed bilateral ptosis, unequal pupils, slowness of movements and indistinct speech. The deep reflexes were present and equal. The ocular fundi were normal. He was discharged on May 16 with the condition unimproved. On the same day he was admitted to a city institution, where he remained for six years. During this time he continued to have both types of attacks. In addition there developed parkinsonian signs, but mentally he remained practically intact.

In August, 1929, the patient suddenly became depressed. He claimed that his food was being poisoned and that the hospital authorities wanted to get rid of him. He heard patients talk about him and make such remarks as "no one should touch his food because it is heavily charged with poison." He also complained to the nurses that he heard children constantly speaking to him. He was depressed. He was sent to a psychopathic ward on September 6. There he was noted to be in an advanced parkinsonian state; he had hallucinations and expressed persecutory ideas.

He was committed to the Manhattan State Hospital on September 12. The physical findings on admission were: stiff gait; head carried forward rigidly; absence of associated movements; some retropulsion; irregular but equal pupils, with sluggish reaction to light and absence of reaction to convergence; bilateral ptosis; divergence of the right eye; hyperactive reflexes in all extremities, more in the left; a Babinski sign on the left side; rigidity in all the muscles; a positive cogwheel phenomenon; fine tremor of the fingers; coarser tremor in the

lower extremities and in the jaw, and tremor of the tongue and of the facial muscles.

There were frequent attacks during which the patient's head would drop on his chest, his knees would give way, and he would slump to the floor, first assuming a squatting and then a supine position. At these times he was unable to speak but knew all that was going on about him. While on the floor the tremor of the jaw and hands decreased markedly and sometimes ceased. During these attacks he was powerless to open his eyes or to move any part of his body. Examination during the attacks showed no change in the reflexes. He also had attacks of sleep which were more frequent than the cataplectic attacks. The latter type of seizures rarely occurred when the patient was lying in bed inactive.

The attacks of sleep occurred while the patient was talking or eating. The eyes would close, the face would take on the expression of repose, and breathing would become deep and slow. The attacks would last three minutes. The patient once fell asleep while opening a drawer, and he was told to open the drawer as soon as he could. He did so on awakening two minutes later. It seems, therefore, that he was aware of the surroundings and of the activities around him during the attacks.

The character of the attacks of sleep apparently had changed from what they were at the onset in 1922. During the patient's residence in the hospital he would occasionally become depressed, but most of the time he was rather dull and apathetic. The persecutory trend faded out gradually.

In July, 1932, the attacks of sleep became more frequent. It was observed that during the attacks the patient would become pale, and the pulse would slow down; on awakening the pulse would become rapid, even tachycardiac. He gradually became very dull mentally, failed to recognize his wife and ceased to talk. He became bedridden and lost considerable weight. He died on Sept. 25, 1932, of septicemia and tuberculosis of the left kidney. The brain is being studied microscopically, and the observations will be reported later.

NARCOLEPTIC ATTACKS IN A CASE OF DEMENTIA PARALYTICA

Case 7.—Joseph G., a man, aged 37, a mason, who was born in New York, and belonged to a macrobian family, had had a normal development, was always robust, and, except for measles, had no diseases of childhood. He received a grammar school education and later learned the trade of a mason. He married at the age of 17. Shortly before he was supposed to have contracted syphilis, but he received no special medication. He was moderate in the use of alcohol but had always been an inveterate smoker. Temperamentally he was active, lively, sociable, easy to become acquainted and to get along with, generous and kind-hearted, a free spender and ready to help those in need.

At the age of 34, the patient began to fall asleep during the day. He fell asleep while talking and during meals; he would fall asleep also at parties, and frequently dozed while hanging on a strap in the subway. He would become irritable when his wife or friends called his attention to his condition. Soon he began to sleep during working hours. He was prevailed on to consult a physician in the fall of 1926. The Wassermann reaction with the blood serum at that time was 4 plus. He received six injections of neoarsphenamine and fifteen of a mercury preparation. Since then he had become forgetful, nervous and irritable and was restless at night; he also became careless about his appearance. He was then sent to a city hospital, where he remained from April 7 to June 18, 1927. While there, he gained considerable weight and seemed to improve mentally. Shortly after dis-

charge from the hospital he began again to fall asleep in the daytime and lost considerable weight. His speech became conspicuously defective, and his libido decreased. He was taken to the Vanderbilt Clinic, New York, where he was given arsphenamine intraspinously, and tryparsamide and mercury. The spinal fluid showed a strongly positive reaction at that time. There were a few neurologic signs, such as a decreased pupillary reaction to light and coarse tremor of the tongue and fingers. The patient continued in the same condition until he entered the Manhattan State Hospital on Nov. 6, 1928, as a voluntary patient. On admission both pupils were irregular in outline, and the right reacted sluggishly to light. The tendon and cutaneous reflexes were very active. Speech was slurred. The spinal fluid contained 2 cells and gave a plus-minus globulin reaction. The Wassermann reaction was 4 plus with both the blood serum and the spinal fluid. Mentally, the patient appeared slightly depressed and underproductive; there were definite memory defects. He was inoculated with malaria on November 19; he had thirteen paroxysms, and was then given quinine. Recovery from the malaria was rather slow; there developed edema of the ankles and numerous abscesses over the body. After several weeks, however, he began to gain weight, became interested and hopeful and began to plan for his future. The Wassermann reaction with the blood serum and spinal fluid became less strong.

In the early part of 1930 the patient was buoyant and hopeful and occupied himself daily. No attacks of sleep were noted at that time. In the later part of 1930 he began to show pronounced evidence of mental deterioration, and at present he is dilapidated, both mentally and physically. For the last year he has been sleeping a great deal during the day.

COMMENT ON THE ETIOLOGIC AND PATHOGENIC POSSIBILITIES

Before discussing the etiology of the attacks of sleep the question whether one is dealing with a state of sleep in these cases should be answered. Redlich,[2c] who has contributed widely to the problem of the narcolepsies, insisted that in the so-called true narcolepsy the sleep is physiologic; he took issue with those who believe that there is a certain preservation of consciousness during the attacks. It seems to us, however, that this controversy is futile, as knowledge regarding the physiology and soundness of sleep is meager. Frequently, the term "sleep" is erroneously used for clouding of the sensorium or comatose states in organic conditions; in cases of neoplasms of the brain it is questionable whether there is a real sleep. In our opinion, it is safer to speak of lowering of conscious awareness in such states.

It is commonly known that sleep may overtake any one for a few minutes after a meal. The continued sleep of infants is well known, as are the sleep states in old age. In certain instances sleep may be considered as a reactive manifestation to some unpleasant situation. It may be also a protective device on the general order of that of the lower animal, who "plays dead" as it were. However, attempts to explain the problem of sleep as a normal manifestation and sleep states in the narcolepsies as pathologic phenomena are futile at present. One need recall only the long discussions concerning normal and pathologic

sleep at the eighth International Neurological Congress in Paris, in 1927, and the meager conclusions reached at that time. The problem is still in the sphere of uncertainty.

In what follows we shall briefly sketch present knowledge or, perhaps better, the assumption of knowledge of the process of sleep.

Shepard [45] suggested the theory of cerebral hyperemia, while others invoked the theory of cerebral anemia as the cause of sleep. Purkinje,[46] in 1846, developed the neurodynamic hypothesis of sleep. According to him, there is an interruption of the conductivity of the nerve centers, with the resulting isolation of the hemispheres and interruption of contact with the outside world. Sleep is also considered to be the result of inhibition, reflex in origin, activated by psychic processes, such as suggestion. All these theories, however, are purely hypothetic, and there is nothing to substantiate them. Adie,[3] in 1926, discussed the theory that sleep is due to action of the inhibitory mechanism of the cerebral cortex. He built up his speculation on the basis of Pavlov's [47] studies of conditioned reflexes. Sleep, according to Pavlov, is due to extensive cerebral inhibition, more than is present during the ordinary conditioned reflexes; the inhibition spreads over the whole cortex and even to subcortical structures. Kleitman and Camille [48] seem to share this opinion.

Periodic asphyxia, excessive production of lipoidolytic substances and the action of lactic acid have been invoked as the cause of sleep. R. Dubois [49] believed that it is an autonarcosis, produced by carbon dioxide. Piéron [50] presupposed the existence of a hypothetic "hypnotoxin," which is supposed to be diffusible, readily oxidized and destroyed by heat. Piéron did not, however, define the chemical nature of this toxin. According to him, "hypnotoxin" is produced during the states of wakefulness, fatigue and exhaustion. Salmon [51] offered the theory of hypophyseal hypersecretion of an antitoxin and of some other substance having an influence on the sympathetic system, producing cerebral anemia and syncope. Chemical studies of the blood during sleep, how-

45. Shepard, J. F.: The Circulation and Sleep, New York, The Macmillan Company, 1914.

46. Purkinje, cited by Claparède.[52] (Original article not found.)

47. Pavlov, I. P.: Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex, translated by G. V. Anrep, New York, Oxford University Press, 1927.

48. Kleitman, N., and Camille, N.: Studies on the Physiology of Sleep: VI. The Behavior of Decorticated Dogs, Am. J. Physiol. **100**:474, 1932.

49. Dubois, R.: Théorie physiologique du sommeil, Rev. scient. **2**:321, 1911.

50. Piéron, Henri: Le problème physiologique du sommeil, Paris, Masson & Cie, 1913.

51. Salmon, A.: Le sommeil pathologique: L'hypersommie, Rev. méd., Paris **30**:765, 1910.

ever, have so far failed to show anything anomalous except perhaps a low calcium and potassium content.

In 1929, Claparède [52] suggested a biologic theory of sleep, according to which sleep is a protective measure to avoid exhaustion. In Claparède's own words: "Ce n'est pas parceque nous sommes intoxiqués, ou epuisés, que nous dormons, mais nous dormons pour ne pas l'être." (We sleep not because we are, but so that we shall not be, intoxicated or exhausted.) Claparède considered sleep as an active, or a reflex, process, and finally as an instinctive process of defense to render the animal inert in order to prevent exhaustion. He stated further that sleep assures the integrity of the great functions of the organism. The seasonal sleep of animals, for instance, results from an instinct of protection or defense. Claparède believed that hysterical sleep is also a phenomenon of defense. We may mention here that Hirsch [53] offered a somewhat similar theory in 1924, when he said that we sleep in order not to become exhausted. Von Economo [54] was in sympathy with this thought.

We wish also to mention the psychodynamic interpretation of sleep offered by the various representatives of the psychoanalytic school. Willey and Rice [55] believed that sleep helps to escape mental conflict; they spoke of a "momentary suicide." According to Freud,[56] Ferenczi [57] and others, sleep represents a return to the nirvana state of the intrauterine life, while awakening symbolizes the painful birth. This return to the intra-uterine state is explained by the necessity of running away every so often from the difficulties of life.

A new approach to the problem of sleep has been made with the advent of epidemic encephalitis. We must, however, mention here that in 1890 Mauthner [58] suggested the presence of a sleep center in the posterior wall of the third ventricle. This was later accepted by Pötzl,[59] by Pette [60] and especially by von Economo.[54] Great significance was

52. Claparède, E.: Le sommeil et la veille, J. de Psychol. norm. et path. **26**: 433, 1929.

53. Hirsch, E.: Zur Frage der Schlafzentren, Med. Klin. **20**:1322, 1924.

54. von Economo, C.: Ueber den Schlaf, Wien. med. Wchnschr. **91**:76, 1926.

55. Willey, M. M., and Rice, A. R.: The Psychic Utility of Sleep, J. Abnorm. Psychol. **19**:174, 1924.

56. Freud, S.: A General Introduction to Psychoanalysis, translated by G. S. Hall, New York, Boni & Liveright, Inc., 1920.

57. Ferenczi, S.: Entwicklungsstufen des Wirklichkeitssinnes, Internat. Ztschr. f. ärtzl. Psychoanal. **1**:124, 1913.

58. Mauthner, L.: Pathologie und Physiologie des Schlafes, Wien. med. Wchnschr. **3**:445, 1890.

59. Pötzl, O.: Zur Topographie der Schlafzentren, Monatschr. f. Psychiat. u. Neurol. **64**:1, 1927.

60. Pette, H.: Die epidemische Encephalitis in ihren Folgezuständen, Deutsche Ztschr. f. Nervenh. **76**:1, 1923.

given to Goltz-Rothmann's dog, which retained the faculty of sleep when the cerebral hemispheres were removed. Pette,[60] Adler [61] and Lucksch [62] hypothecated the existence of a sleep center from observing attacks of sleep in cases of lesions of the midbrain. Trömner [41] placed the sleep center in the thalamic region, and Redlich [2c] believed that the center must be somewhere between the diencephalon and mesencephalon, near the third ventricle.

Marinesco [63] considered sleep as a disturbance of tonus, and Stern [64] attempted to explain the phenomenon as a blocking of the passage of tonus from the cerebellum to the cerebrum. These hypotheses will hardly stand, since knowledge of tonus is anything but complete.

Hess [65] produced sleep by electrical stimulation of the hypothalamic region. Demole [66] obtained the same results by injecting calcium into the brain. Serejski [16] produced immediate sleep by the injection of calcium chloride into the para-infundibular region; when he injected calcium into the thalamus sleep set in from five to ten minutes later and was light. Serejski believed that there is an immobilization of calcium in the brain during sleep, but this is only an assumption.

Neurologists often observe sleep states in persons suffering from hypophyseal tumors. In this connection it is worth mentioning that Jolly,[67] Kahler,[36] Janzen,[68] Stiefler,[69] Singer [5] and others emphasized the smallness of the sella turcica in their cases of narcolepsy. On the other hand, in the cases of Dercum,[70] Mendel,[71] Hilpert [72] and Henne-

61. Adler, Edmund: Zur Lokalisation des Schlafzentrums, Med. Klin. **20**: 1321, 1924.

62. Lucksch, F.: Ueber das Schlafzentrum, Ztschr. f. d. ges. Neurol. u. Psychiat. **93**:93, 1924.

63. Marinesco, G.; Sager, O., and Kreindler, A.: Beiträge zu einer allgemeinen Theorie des Schlafes, Ztschr. f. d. ges. Neurol. u. Psychiat. **122**:23, 1929.

64. Stern, Felix: Die epidemische Encephalitis, Berlin, Julius Springer, 1922.

65. Hess, W. R.: Lokalisatorische Ergebnisse der Hirnreizversuche mit Schlafeffekt, Zentralbl. f. d. ges. Neurol. u. Psychiat. **54**:325, 1929-1930.

66. Demole, V.: Pharmakologisch-anatomische Untersuchungen zum Problem des Schlafes, Arch. f. exper. Path. u. Pharmakol. **120**:229, 1927.

67. Jolly, P.: Ueber Narkolepsie, Deutsche Ztschr. f. Nervenh. **55**:236, 1916.

68. Janzen, E.: Ueber Narkolepsie (Gélineau-Redlich), Ztschr. f. d. ges. Neurol. u. Psychiat. **104**:800, 1926.

69. Stiefler, G.: Ein Fall von genuiner Narkolepsie, Neurol. Centralbl. **37**: 380, 1918.

70. Dercum, F. X.: Profound Somnolence and Narcolepsy, J. Nerv. & Ment. Dis. **40**:185, 1913.

71. Mendel, K.: Kriegsbeobachtungen: Narkolepsie, Neurol. Centralbl. **35**: 359, 1916.

72. Hilpert, P.: Ueber einen Fall von Narkolepsie, Klin. Wchnschr. **2**:1553, 1926.

berg [7] the sella was very large. In Henneberg's [7] case there were acromegalic features. Redlich's 3 cases and the cases of Stiefler [69] and Dercum [70] showed various unusual secondary sex characteristics. Dana [23] described features of acromegaly, dystrophia adiposogenitalis and dyspituitarism in his cases. Bychowsky [73] and Stewart [74] described states of somnolence in cases of hypophyseal tumors. Forster [75] and Zador [76] reported narcoleptic attacks and a change to a heterotype of secondary sex characteristics after oophorectomy. Wilder [77] made a similar observation following castration.

It is of interest that Rosenthal [43] and Redlich [2c] found a low basal metabolic rate in their patients with narcoleptic attacks, while Wenderowic [6] and Sperling and Wimmer [78] found a high rate. Particular attention should also be paid to the lymphocyte count in certain narcoleptic persons: Redlich [2c] found a lymphocytosis of about 49 per cent in 4 cases and of 30 per cent in 2 other cases. Similar findings were reported by Stiefler,[69] Kahler [36] and others.

Lhermitte and Tournay [10] observed narcoleptic attacks in cases of status lymphaticus. Thiele [79] emphasized the significance of increased frequency of attacks during puberty; Fischer,[34] Ballet [35] and Kahler [36] during menstrual periods and Balogh,[80] Nevermann [81] and Gruszecka,[82] during pregnancy. These authors seem to emphasize the possible relationship of normal sleep and the so-called pathologic sleepy states to the activity of the endocrine apparatus, especially of the hypophysis. Changes in the pituitary gland of hibernating animals during the winter months are also known (Cushing and Goetsch [83]). However, one must

73. Bychowsky, G.: Ueber einen Fall periodischer Schlafsucht mit anatomischem Befund, Deutsche Ztschr. f. Nervenh. **78**:113, 1923.

74. Stewart, P.: Four Cases of Tumor in the Region of the Hypophysis Cerebri, Rev. Neurol. & Psychiat. **7**:225, 1909.

75. Forster: Narkolepsie, Zentralbl. f. d. ges. Neurol. u. Psychiat. **48**:730, 1927-1928.

76. Zador, J.: Ein Fall von „symptomatischer" Narkolepsie mit experimenteller Auslösbarkeit der Anfälle, Monatschr. f. Psychiat. u. Neurol. **66**:13, 1927.

77. Wilder, J.: Untersuchungen an einem Kastraten mit transplantiertem Affenhoden. (Hoden und vegetatives Nervensystem: Kastration und Narkolepsie), Ztschr. f. d. ges. Neurol. u. Psychiat. **117**:472, 1928.

78. Sperling, O., and Wimmer, R.: Zur Kasuistik und Auffassung der Narkolepsie, Deutsche Ztschr. f. Nervenh. **102**:252, 1928.

79. Thiele, R.: Zwei Fälle von Narkolepsie mit Lachschlag, Zentralbl. f. d. ges. Neurol. u. Psychiat. **46**:904, 1927.

80. Balogh, M.: Narcolepsie During Pregnancy, Orvosi hetil. **68**:203, 1924.

81. Nevermann, H.: Ueber Narkolepsie in der Schwangerschaft, Deutsche med. Wchnschr. **47**:1164, 1921.

82. Gruszecka, A.: Narcolepsy, Polska gaz. lek. **7**:170, 1928.

83. Cushing, H., and Goetsch, E.: Hibernation and the Pituitary Body, J. Exper. Med. **25**:22, 1915.

consider all these hypotheses as premature and speculative, as present knowledge of the function of the endocrine apparatus and its central representation is inadequate.

The manifestations of affective loss of tonus are not always pathologic phenomena in a strict sense. Sudden loss of muscular tonus may occur in people who are otherwise not subject to narcoleptic attacks. It is the experience of many observers, and of ourselves, that fright or embarrassment may produce in many normal people muscular weakness lasting a moment or so. We once observed a professional man who while delivering an address became visibly weak in the knees when some one in the audience coughed loudly. Women occasionally become incontinent while laughing. Homeric laughter may produce general weakness, and the Germans speak of *zum Tode lachen*. In the most severe form these attacks are known under the name of *Lachschlag* (Oppenheim [84]), and there is frequently a complete loss of consciousness.

It must be admitted that the pathogenesis of the attacks of affective loss of muscular power is just as involved and obscure as that of the attacks of sleep. Here again changes in the midbrain and in the hypothalamic region are invoked for the explanation of the attacks. This is made on the basis of observation of cataplectic attacks in cases of chronic epidemic encephalitis and cases of pituitary disturbances. It is of interest that long before the advent of epidemic encephalitis Bechterew [85] linked the optic thalamus with expression of the motor manifestations of affect. He considered, for instance, mimetic facial paralysis as due to a lesion in the thalamus. Forced laughter and crying are at present linked with lesions in the striate body. Jakob [86] and F. H. Lewy [87] claimed the existence of "tonus inhibitory centers" in the subcortical ganglia. In striatal disease, especially with parkinsonism, the increase of tonus is explained by a falling out of the tonus inhibitory function. Redlich [2c] believed that under the influence of vivid affects a sudden increase of tonus inhibition occurs, with a resulting sudden general or partial loss of tonus. Von Economo,[54] Lewy [87] and Jakob [86] believed that there is considerable evidence that the basal ganglia are associated with affect. They also believed that the proximity of the basal ganglia to

84. Oppenheim, H.: Ueber Lachschlag, Monatschr. f. Psychiat. u. Neurol. **11**: 242, 1902.

85. Bechterew, U. M.: Die Funktionen der Nervzentra, Jena, Gustav, Fischer, 1909.

86. Jakob, A.: Die extrapyramidalen Erkrankungen mit besonderer Berücksichtigung der pathologischen Anatomie und der Histologie und der Pathophysiologie der Bewegungsstörungen, Berlin, Julius Springer, 1923.

87. Lewy, F. H.: Die Lehre vom Tonus und der Bewegung: Zugleich systematische Untersuchungen zur Klinik, Physiologie, Pathologie und Pathogenese der Paralysis agitans, Berlin, Julius Springer, 1923.

the periventricular gray matter makes a transition of sleep to cataplexy and vice versa easily understood, through an overflow of stimulation.

Lhermitte and Tournay [10] suggested a theory of dissociation of the two main elements of sleep for the explanation of the cataplectic attacks. According to these authors, there is a weakening of the static tonus such as is seen in deep sleep while the sensorium remains clear. That brings the whole problem back to the question of normal sleep.

THE RELATIONSHIP OF THE NARCOLEPSIES TO THE EPILEPSIES

As was stated in the introductory paragraphs there is reason to believe that there may be some relationship between the narcolepsies and the epilepsies. F. Fischer,[88] in 1878, was impressed with certain epileptoid features in his case and believed that both his and Westphal's [87] cases were epileptoid. Other investigators made similar observations later. Noack's [89] patient made peculiar movements with his head and protruded his tongue. Goldflam [38] observed twitches, and Kahler [36] was impressed with hyperkinetic manifestations during the attacks of sleep. Redlich [2c] noted ticlike movements during the narcoleptic attacks, but denied the presence of the so-called epileptoid trait in narcolepsy. It is important, however, to note that Redlich was one of the few who was able to elicit the Babinski sign after an attack. Kraepelin [15] was rather inclined to believe in a close relationship between the two entities. Of the most recent investigators, Serejski and Frumkin [16] believed that the narcoleptic attack is a form (equivalent) of the epileptic seizures. In support of their contention they emphasized the slight confusional states occasionally seen after narcoleptic attacks. They also mentioned the irritability, night wanderings and alcoholic intolerance noted in persons suffering from narcolepsy. Like Goldflam,[38] they noted hyperkinesis during the attacks. Various types of aura are described by Goldflam,[38] Hilpert,[72] Strauss,[90] Fischer,[88] Noack,[89] Münzer [91] and others. Adie,[3] Redlich,[2c] Curschmann and Prange [39] and a few others have disputed the close relationship to the epilepsies, pointing out that epileptic attacks occur spontaneously while narcoleptic attacks are emotionally determined. This is an erroneous conception; one has only to consider the common "affect epilepsy" to dispel the notion that epileptic attacks are always spontaneous

88. Fischer, F.: Epileptoide Schlafzustände, Arch. f. Psychiat. **8**:200, 1878.

89. Noack: Narkolepsie, Neurol. Centralbl. **37**:27, 1918.

90. Strauss, H.: Zur Kasuistik und Auffassung der Narkolepsie, Monatschr. f. Psychiat. u. Neurol. **61**:265, 1926.

91. Münzer, F. T.: Zur Frage der symptomatischen Narkolepsie nach Enzephalitis lethargica, Monatschr. f. Psychiat. u. Neurol. **63**:97, 1927.

(Notkin [92]). It is of interest to mention that Lewy [93] has reported a case with apparent cryptogenic epileptic attacks provoked by laughter. Similar cases were also observed by Binswanger.[94] It is also important to note that cataplectic attacks are known to occur spontaneously in the absence of any affect (Rapoport [95]). As was stated, cases are reported in the literature with a mixture of both narcoleptic and epileptic attacks or with a transition of one form of attacks into the other. Mendel [71] reported a case of epileptic attacks up to the age of 22 with a change to narcoleptic seizures from that age on. Goldflam's [38] patient had at first narcoleptic attacks for six years and since then only epileptic seizures. Féré [96] and others reported cases in which there were both sleep and epileptic attacks. The question of deterioration can hardly be taken into consideration, since it is known that only a small percentage of epileptic persons do ultimately deteriorate. There has also occasionally been reported a positive epileptic heredity in cases of narcolepsy. Narcoleptic and epileptic attacks may occur in members of the same family (Wilson [9] and Heveroch [97]).

All facts considered, one cannot disregard the possibility that these are closely related manifestations. This relationship may be resolved satisfactorily when more patients have been completely analyzed at the physicochemical, sensorimotor and symbolic levels. Research should be carried out at all three levels of the integrated individual.

SUMMARY

Cases of attacks of sleep were described long before the *nomen morbis* was coined by Gélineau.

Narcolepsy is not a disease per se, but a group of symptoms that may occur under a variety of conditions.

The cases reported in the literature can be classified in five definite groups: (1) attacks of sleep and hypersomnia in psychoneuroses, in manic-depressive psychoses and in schizophrenia; (2) narcoleptic attacks in chronic epidemic encephalitis; (3) narcoleptic attacks in cases of involvement of the central nervous system, exclusive of group 2, and in cases of somatic disease; (4) attacks in combination with convulsive

92. Notkin, J.: "Affectepilepsy" and "Hysteroepilepsy": A Study of Convulsive States in Psychopaths, J. Nerv. & Ment. Dis. **72**:135, 1930.

93. Lewy, E.: Beitrag zur Nosologie epileptischer Anfälle, Ztschr. f. d. ges. Neurol. u. Psychiat. **110**:235, 1927.

94. Binswanger, O.: Die Epilepsie, in Nothnagel, C. W. H.: Spezielle Pathologie und Therapie, Vienna, Alfred Hölder, 1899.

95. Rapoport, M. J.: Zur Klinik der Kataplexie, Psychoneurologische Festschrift für A. J. Iuschtschenko, Nord Caucasus, 1928, 295.

96. Féré, C.: Note sur l'apathie épileptique, Rev. méd. **11**:211, 1891.

97. Heveroch, A.: Narcolepsia, Časop. lék. česk. **63**:1477, 1924.

(epileptic) attacks; (5) attacks in cases in which there are no definite signs pointing to organic pathologic changes.

The cases in group 5 are designated as the cryptogenic type of narcolepsy.

Seven personal observations of the symptomatic and cryptogenic types are described.

The symptom complex is discussed. It is believed that only in the cryptogenic group are both types of attacks, the narcoleptic and the cataplectic, present, while in the symptomatic variety one or the other type of seizures is prevalent.

A review of the current theories of the process of sleep is made.

The etiologic and pathogenic possibilities are discussed, and it is suggested that the narcolepsies are closely related to the epilepsies. This supposition is made on the bases of the following considerations: (1) the paroxysmal nature of the narcoleptic attacks; (2) the occasional occurrence of various types of aura preceding the attack; (3) the hyperkinetic manifestations reported during the narcoleptic attacks; (4) the confusional states reported at times as following the attacks; (5) the mixture of both types of attacks—the narcoleptic and the epileptic—in the same person; (6) the occasional transition of narcoleptic manifestations into epileptic seizures and vice versa; (7) the epileptic heredity in some instances; (8) the fact that similarly to the epilepsies there are the symptomatic and the cryptogenic types of narcolepsies.

The Main Afferent Fiber Systems of the Cerebral Cortex in Primates: An Investigation of the Central Portions of the Somato-Sensory, Auditory and Visual Paths of the Cerebral Cortex, with Consideration of Their Normal and Pathological Function, Based on Experiments with Monkeys. By Stephen Poliak, M.D., Associate Professor of Neurology, University of Chicago. University of California Publications in Anatomy, Volume 2. Price, $10. Pp. XIV and 370, with 96 figures in text. Berkeley, Calif.: Univ. California Press, 1932.

This fine monograph is really a preliminary, and a necessary, one to a study of the comparatively little known association connections of various cortical areas as determined by cyto-architectural and myelo-architectural investigations. Obviously an accurate knowledge of the afferent projection systems is a necessary basis for an anatomic study of the association systems by which impulses received by the cortex are, so to speak, spread to other cortical regions or mechanisms. As the author points out, such knowledge has not been attained as yet. The two principal problems in attaining such knowledge are, first: disclosing the anatomic identity of functionally distinct afferent paths from their peripheral receptor organs to their cortical terminations and, second, establishing the internal organization of the afferent paths. Only after these problems have found a satisfactory solution can an attack be made on the following question: By what paths and mechanisms are the impulses streaming into the cortex distributed and combined to form higher, complex forms of cortical activity? If the latter and more difficult problem can be solved, an anatomic basis will be furnished for a proper understanding of cortical functions.

In a broad sense, those who differ in opinion concerning afferent cortical projection and the interpretation of its meaning and of cortical function fall into the two well known groups of "localists," who adhere to the view of circumscribed limited areas and of spatial representation within these areas, and those who believe in more diffuse projection and lack of definite spatial localization, i. e., in an equipotentiality of all parts of the cortex or something approaching it. The latter view is apparently more favorable to the requirements of the *Gestalt* school of psychology. It is obvious that if definite localization of afferent projection fibers is established, more or less definitely

localized association areas in especially close connection with these will probably be ascertained, which will in turn favor the localization to some extent, at least, of higher cortical functions. Such localization, in gross, at least, of primary afferent projection areas is accepted by the majority of neurologists, but there are important disagreements even here, and there is still more disagreement with respect to more minute localizations within each principal projection area.

Some of these differences in views are pointed out by the author. In regard to the somatosensory area, some restrict this to the postcentral part of the cortex and believe that it does not overlap the precentral cortical region, thus holding to a complete separation of the sensorium from the motorium (dualistic view), while others extend the sensorium over the precentral motorium. There are also differences of opinion as to the caudal boundary of the sensorium. In regard to the auditory region, there is uncertainty as to whether the primary projectional auditory cortex is a small well defined area or whether it extends over a considerable portion of the temporal cortex. The complicated problems and contradictory views arising in regard to aphasia are concerned in the solution of this question. Concerning the visual projection system, there are the views of those who believe in the existence of projections from three subcortical centers (the roof of the midbrain, the pulvinar thalami and the external geniculate body), a multiple cortical representation of the retina, including even the macula, and no correspondence between the retinal segments and the cortical areas. Opposed to this is the view which is supported by the majority of neurologists and which has been confirmed in most details by experiences in the war—that the central visual path has its only subcortical origin in the external geniculate body, forms a definite fiber system of the hemisphere and the external or lateral sagittal stratum of the parieto-occipital lobe and has its exclusive cortical termination in the striate area of Elliot Smith, field 17 of Brodmann and area OC of von Economo and Koskinas. The pathologic control in human material is, however, quite scanty, according to the author, and there are still important dissenters. There are also important points to be cleared up concerning the paths from various parts of the retina, especially the macular path, among which may be mentioned, in relation to the sparing of macular vision in certain cases of homonymous hemianopia, the question of a cortical decussation of part of the macular path. In general, in a study of the internal organization of the visual path, there is the question whether the paths from various parts of the retina are projected on distinct, mainly nonoverlapping areas in the visual cortex or whether there is no such regular spatial arrangement but diffuse overlapping terminations.

EXPERIMENTS

In order to obtain results which might be applicable to human physiology and pathology, the experiments were carried out on monkeys (*Macacus rhesus,* except in one instance, in which a Java monkey was used). The experiments consisted of interruptions of the afferent projection fiber systems at or near their origin in the thalamencephalon, thereby causing their partial or complete secondary degeneration and avoiding at the same time, so far as possible, other fiber systems. The secondarily degenerated fibers were traced to their respective terminations in the cortex, and the internal arrangements of the three afferent paths which were investigated (somatosensory, auditory and visual), the cortical areas in which they terminated and the finer relation of their fibers to the cortex were studied. The staining method used was the osmic acid method of Marchi, which displays the fibers, in a certain stage of degeneration, stained black against a light field. It seems to me that the possibility of retrograde degeneration of myelinated fibers forming part of the Marchi pictures might have been discussed by the author, although the figures do not lend themselves to this possibility.

The site of entrance of the instrument is shown in drawings of the brain, and the course of the lesion is described and is also shown in the drawings of sections. The outlines of the lesions and the resulting degeneration, as seen in the sections, are shown in about seventy-one fine drawings, in which orientation is materially assisted by the fact that the normal fibers are also shown in a light color. The cortical areas on which the various systems of afferent fibers are projected are shown in figures in the text. Although it seems like asking too much, in view of the fine and profuse illustrations, it would add to clarity if drawings of reconstructions in toto of the various lesions and adjacent structures could have been added, or at least some outline of their boundaries projected on sagittal views of the brains.

Experiments were also made with a view to ascertaining, in sections stained by Nissl's method, the cells in the external geniculate body from which various portions of the visual radiation originate. This method takes advantage of the well known changes manifested in nerve cell bodies the axons of which have been cut, which are known as primary irritation of cells or retrograde degeneration. In this case lesions of various parts of the visual cortex were made, and the resulting changes in the cells of the external geniculate body were studied.

Conclusions regarding the three afferent paths investigated were obtained from eleven experiments; brief mention is made of twenty-five other experiments.

It was found incidentally to the main investigation that some of the lesions appeared to show that all fillet and spinothalamic tract fibers

terminate in the thalamus, none passing beyond to the cortex, thus further confirming the generally accepted view, and that probably the afferent thalamopetal tracts do not occupy merely a narrow zone beside the external medullary lamina but are distributed to the entire lateral nucleus of the thalamus.

THE SOMATIC SENSORY SYSTEM

In four experiments, so far as the somatic sensory system was concerned, the attempt was made to interrupt the thalamocortical radiation by injuring the thalamus or by cutting the radiation itself close to the thalamus. In one experiment this was done almost entirely by an intrathalamic lesion; in a second experiment the thalamocortical radiation was interrupted chiefly within the internal capsule in the immediate vicinity of the thalamus, partly by an intrathalamic lesion; in a third and a fourth experiment a portion of the radiation was interrupted within the internal capsule exclusively. In the first experiment a large part of the radiation degenerated; in the second, probably the greatest part, if not all, of the radiation; in the third, only the posterior or caudal half, and in the fourth, only the intermediate segment. The object of these experiments was, primarily, to determine the minimal cortical region of the hemisphere which was supplied by fibers of thalamic origin; also to determine the origin, course and termination of parts of the thalamocortical radiation, as well as to delimit cortical areas where such individual bundles of the radiation terminate and to study the minute relation of the afferent fibers to cortical structures.

Without entering into the comparison made by the author of the areas receiving degenerated fibers with the cyto-architectural areas determined by Brodmann in *Cercopithecus,* the interesting result was obtained that the somatosensory cortical area included a large precentral as well as postcentral area. This finding agrees partly, but only partly, with the unitarian view of a functionally uniform "sensomotorium" and disagrees with the views which are probably most widely accepted at present, i. e., that the somatosensory area is wholly postcentral. On the other hand, by comparing the somatosensory area with the auditory and visual areas, as determined by the same research, it is evident that considerable areas separate these and are therefore apparently destitute of afferent projection fibers. These findings approach the view of Flechsig that large cortical areas are solely "association" areas.

Another interesting result, which is not dissimilar to the conclusions reached by E. Sachs, which are also indicated by dissection, is that the areas vary in position corresponding with the position of the lesion; e. g., where the lesion extends farther orally the area extends similarly. In the fourth experiment, in which a well defined smaller intermediate lesion was made at the genu of the internal capsule, the resulting degen-

erated fibers were confined to a corresponding well defined intermediate cortical area. This leads to the conclusion that the radiation may be best conceived as a series of fans approximately perpendicular to the long axis of the hemispheres and arranged in a caudorostral series. Another point is the fact that the afferent projection fibers are most dense around the central sulcus ("nuclear" or "focal" zone). From this region their density gradually diminishes toward the posterior or caudal and anterior boundaries of the somatosensory area.

On entering the cortex, the degenerated fibers do not usually form part of the bundles of the radiation, which are composed principally of the axons of the local cortical cells, but have an oblique or horizontal course. They finally enter and principally terminate in the stripes of Baillarger. There are no gaps or islets in the supply of thalamic fibers to the area. The intracortical somatosensory fibers are somewhat coarser than those of the visual radiation. None cross in the corpus callosum. Comparisons are made by the author with the cyto-architectural areas of Brodmann and other investigators.

The author discusses the possible functions of the somatosensory area. He does not regard the entire area as a functionally uniform "sensomotorium," as he thinks that this view is negatived by the various structural differences within the area, but he believes that his investigations "clearly demonstrate that some form or other of the receptive, somato-sensory function has to be attributed also to the precentral agranular cortex."

Certain experimental work (Ranson and Cushing's on man, and Minkowski's and Dusser de Barenne's on monkeys) is cited as showing the possibility of a sensory function in this precentral portion, also the possibility of a form of "unconscious reflex sensibility." The author also raises the question whether different forms of sensibility are represented in different cyto-architectural areas or, perhaps, in different layers of the entire somatosensory cortex, and he thinks that "each precentral and postcentral cyto-architectural area is endowed with its own special component of a primitive, elementary quality of sensibility not identical with that of other somato-sensory areas." The problem presented in this respect by the somatosensory area is different from that of the visual and auditory areas, as the latter are unisensory, having to do with only one quality of sensation, whereas the somatosensory is multisensory. The other suggestion that different forms of sensibility are represented in different layers of the entire somatosensory area would seem to be negatived by the presence of similar layers in other parts of the cortex.

THE CORTICOFUGAL FIBERS

The author's experiments also demonstrate various corticofugal fibers. Regarding an extensive corticothalamic system, he is somewhat

reserved, though he does not deny its existence. The bulk of the fibers which degenerate after the destruction of the occipitoparietal cortex and which enter the caudal portion of the thalamus, especially of the pulvinar thalami, certainly reach the midbrain by way of the brachium of the superior colliculus. The latter system apparently does not originate in the area striata; it forms a part of the internal sagittal stratum, and in the superior colliculus it forms mainly the superficial medullary stratum, and, to a lesser extent, the intermediate and zonal strata.

Other numerous corticofugal fibers descending from the precentral and frontal cortical regions are: (1) numerous fine fibers to the caudate nucleus by way of the subcallosal stratum and the internal capsule; (2) numerous somewhat coarser fibers to the globus pallidus, entering by its dorsal extremity; (3) fairly thin fibers to the tegmental nucleus; (4) fairly coarse and medium-sized fibers to the stratum intermedium of the peduncle and substantia nigra, extending as far caudalward as the substantia extends and descending partly by way of the median fillet, and (5) the well known corticospinal, corticobulbar fibers and numerous association and callosal fibers. Conclusions 1 and, especially, 2 are not in accordance with perhaps the most generally accepted view and are very important if substantiated.

THE AUDITORY SYSTEM

The auditory radiation at first, i. e., near its origin from the internal geniculate body, closely accompanied by ventral bundles of the thalamocortical radiation, enters the most ventral part of the internal capsule. It crosses above and somewhat in front of the visual radiation where the latter forms the triangular area of Wernicke. It cuts partly through the brim of the putamen and passes partly caudad to it. Farther laterally it enters at first the stratum sagittale of the temporal lobe, forming that portion of it close beneath the claustrum, and then turns gradually to the cortex. Its fascicles have a regular spatial arrangement; the most dorsal and caudal enter the cortex first in the posterior corner of the sylvian fossa, and the ventral bundles continue to the more oral segments of the auditory cortex. This regular arrangement indicates a similar spatial arrangement of the cortical areas on which the fascicles are projected. No fibers cross to the other hemisphere in the corpus callosum.

The cortical area supplied by the auditory radiation is the upper half of the superior temporal convolution and only that. Only a few fibers reach the free surface of the temporal lobe. The most richly supplied portion is a small zone in the posterior corner of the sylvian fossa where there is an elevation comparable with the transverse temporal convolution of Heschl in man. This zone represents the "nuclear or focal zone" of the auditory cortex.

The author concludes from the spatial arrangement of the cochlear fibers that there is a spatially arranged system for the conduction of various tones and has made an interesting attempt to explain the minute function of the auditory system, based on the arrangement of the direct and spiral cochlear nerve fibers.

THE VISUAL SYSTEM

Of the three systems, the visual receives the most attention. The conclusions are arrived at by comparing the results of more extensive and partial lesions, which appear to show clearly the spatial arrangement stressed by the author in his summary. Quite remarkable is the strict correspondence of the distribution of the visual fibers with the area striata, and it is also interesting to note the confirmation of the views of Ramón y Cajal, based on Golgi preparations, as to the layers receiving the exogenous visual fibers, i. e., the various sublayers of the stripe of Gennari.

Following is the summary, with some minor omissions, by the author of the results deduced from his detailed description of the visual system:

1. The external geniculate body of the between-brain must be recognized at present as the only and the exclusive origin of the visual radiation in primates.

2. There exists only one single direct afferent visual path from the subcortical region to the cerebral cortex. (Nothing positive is known of indirect visual paths.) It is the fiber system originating from the external geniculate body. That external geniculo-cortical radiation forms a strong fiber lamina or layer identical with the "primäre Sehstrahlung" of Flechsig, with the stratum sagittale laterale of H. Sachs, a portion of which was called by Burdach, Wernicke, and Monakow "fasciculus longitudinalis inferior" of the parieto-occipital and temporal lobes. However, other fibers: efferent, callosal, and associational, mix with the afferent visual fibers. Stratum sagittale internum, "sekundäre Sehstrahlung" of Flechsig, is an efferent fiber system. The tapetum is composed exclusively of callosal fibers.

3. The cortical region where the visual path terminates is a single, definite, and sharply delimited area which is identical with the area striata of G. E. Smith, field 17 of Brodmann, or area OC of Economo-Koskinas distinguished by the strong intracortical fiber layer, the stripe of Gennari or Vicq d'Azyr (fig. 1). No other areas of the cerebral cortex receive afferent visual fibers.

4. The central visual path above the external geniculate body is strictly unilateral. No evidence exists of a partial decussation of its fibers through the corpus callosum ("fasciculus corporis callosi cruciatus"). The only spot, therefore, where the visual path undergoes a partial decussation is below the between-brain in the optic chiasm.

5. The fibers of the visual radiation are, on the whole, finer than the somatic sensory (thalamo-cortical) fibers. Most of the visual fibers are of medium size, only a small number having a large caliber. The coarse visual fibers almost exclusively enter the fissura calcarina and the pole of the occipital lobe; the thin or medium sized fibers enter the pole of the occipital lobe and the occipital operculum. The visual fibers, however, exceed in caliber the association and callosal fibers of the striate area and of the occipital lobe generally.

6. The visual radiation is composed of fibers grouped into fiber bundles arranged, on the whole, in parallel fashion. Each fiber bundle originates in a definite small segment of the external geniculate body and terminates in a definite small segment of the striate area.

7. The visual radiation or the external sagittal layer of the parieto-occipital lobe can be subdivided into three anatomical-functional portions discernible on cross-sections perpendicular to the long axis of the hemisphere: (*a*) the dorsal horizontal branch, (*b*) the ventral horizontal branch, and (*c*) the vertical or the perpendicular branch connecting both horizontal branches. The dorsal horizontal branch is composed of fibers originating in primates from the medial (internal) segment of the external geniculate body close to the thalamus which corresponds with the upper extramacular segments of both homonymous hemiretinae, including the upper monocular portion of the crossed retina. This branch supplies the striate cortex of the upper (dorsal) lip of the fissura calcarina. . . . The ventral horizontal branch [not injured in any of the author's experiments] is

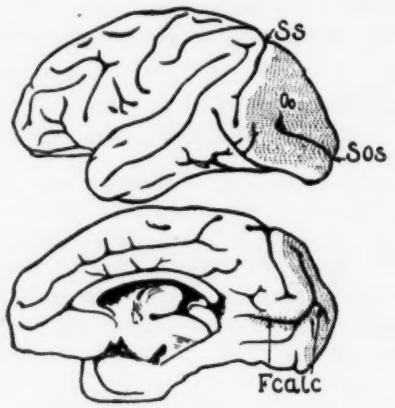

Fig. 1.—Diagram showing the position and extent of the visual projection cortex in the brain of the monkey, as determined in the present investigation. This area is identical with the area striata of Elliot Smith, or Brodmann's field 17, both on the lateral face (upper drawing) and on the medial face (lower drawing) of the hemisphere. In the monkey the striate area along the undivided horizontal branch of the calcarine fissure (*Fcalc*) remains hidden in the fissure, emerging on the surface only along the ascending and descending branches. Over the convex face of the occipital lobe it extends over the greater part of the occipital operculum (*Oo*) behind the simian sulcus (*Ss*) and is divided into two unequal portions, an upper and a lower one, by the superior occipital or external calcarine sulcus (*Sos*).

composed of fibers originating from the lateral (external) segment of the external geniculate body close to the lentiform nucleus, corresponding with the lower extramacular quadrants of both homonymous hemiretinae, including the lower monocular portion of the crossed retina. It supplies the striate cortex of the lower (ventral) lip of the fissura calcarina. The narrow zones of the striate area supplied here are probably similarly arranged longitudinally, as are those in the upper lip, but in reverse order, with the most medial zones being supplied by the most ventro-medio-anterior bundle, and so forth. The perpendicular (intermediate)

branch of the visual radiation is composed of fibers originating from the large intermediate segment of the external geniculate body, which is situated between both internal and external segments of that body. This intermediate segment corresponds to both dorsal and ventral quadrants of both homonymous hemimaculae. The vertical branch represents a considerable portion, probably more than half, of the visual radiation. It supplies the striate cortex covering the pole of the occipital lobe, and in the monkey, as far as the striate cortex extends, the external face of the occipital lobe or the so-called operculum occipitale. The vertical branch represents in its upper half, near the dorsal horizontal branch, the upper quadrants of both homonymous hemimaculae; in its ventral half, near the ventral horizontal branch, the lower quadrants of both homonymous hemimaculae (fig. 2).

8. In view of the above statements and the results of pathological and experimental studies of Rönne (1914) and of Brouwer-Zeeman (1926), the following conclusions as to the projection of the retina upon the cortex in primates and in man (fig. 3) must be made.

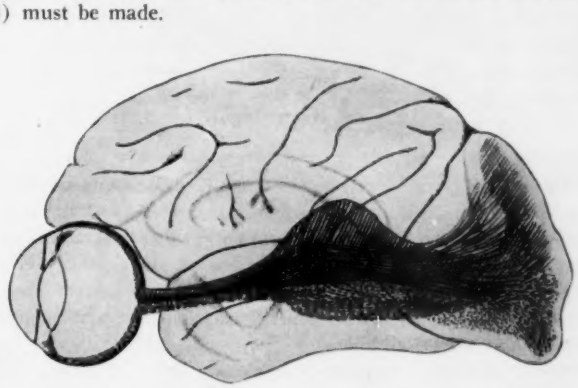

Fig. 2.—Course and arrangement of the entire afferent visual path from its beginning in the retina of the eye (left in the figure) to its termination in the occipital lobe (right in the figure) in the right hemisphere of the brain of Macacus viewed from the internal side and imagined transparent. In the retina, the optic nerve and optic tract, the external geniculate body and the visual radiation, the area of broken lines corresponds to the lower extramacular quadrants; the dotted area, to the lower macular quadrants; the area of diagonal lines, to the upper extramacular quadrants, and the area of continuous lines to the upper macular quadrants. In the external geniculate body and in the visual radiation the relative position of the various bundles corresponds to their position as found in the present investigations (combined with those of Brouwer and Zeeman). The upper and lower extramacular fibers enter the upper and lower lip of the calcarine fissure, respectively; the macular fibers interposed between both extramacular bundles enter the pole of the occipital lobe and the operculum occipitale.

(*a*) The upper extramacular quadrants of both homonymous hemiretinae (lower quadrants of the homonymous halves of the visual fields with exclusion of the macular portion), together with the upper half of the monocular portion of the crossed retina (lower half of the crossed temporal crescent) are projected upon the upper lip of the fissura calcarina (in man, anterior portion of that lip).

(*b*) The lower extramacular quadrants of both homonymous hemiretinae (upper quadrants of the homonymous halves of the visual fields with exclusion

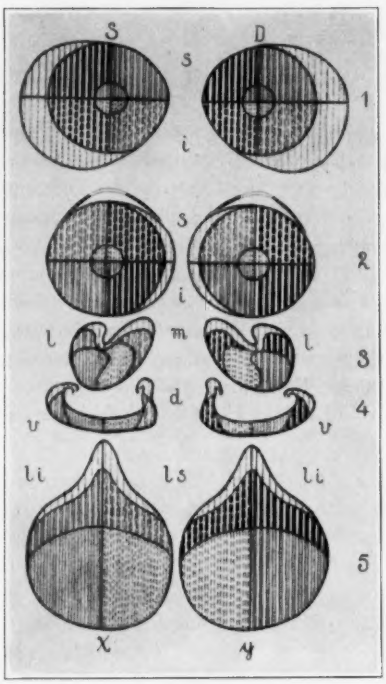

Fig. 3.—Diagram illustrating the projection of various quadrants of the visual fields and of both retinas on the external geniculate bodies, the visual radiation and the visual projection area of the cerebral cortex (area striata), as determined by the present experiments combined with those of Brouwer and Zeeman. The left sides of the visual fields and of the afferent visual apparatus are indicated by *S;* the right, by *D*. *1* represents both fields of vision with their upper (*s*) and lower (*i*) nasal and temporal halves. The smaller inner circles represent the central or macular portions. (Their relative size in comparison with the perimacular portion is somewhat exaggerated.) The large circles represent the perimacular or extramacular portions of the binocular visual fields; the outermost, lightly shaded sickle-shaped zones represent the monocular portions of the visual fields. *2* represents the left and right retinas with their upper (*s*) and lower (*i*) nasal and temporal halves. The smaller and larger circles and the sickle-shaped zones have the same indication as in *1*. *3* represents a schematic cross-section through the left and right geniculate bodies. The internal margins, close to the thalamus, are indicated by *m;* the external margins, by *l*. The concave contours facing upward represent the ventral margins. *4* represents cross-sections through the left and right visual radiation (external sagittal strata of the parieto-occipital lobes). The dorsal horizontal branches are indicated by *d;* the ventral horizontal branches, by *v*. Perpendicular or vertical (in the figure, horizontal) branches connect both horizontal branches. *5* represents the left and right visual projection cortex, the area striata of Elliot Smith and field 17 of Brodmann. Each is subdivided into an upper (*ls*) and a lower (*li*) half, corresponding with the upper and lower lips of the calcarine fissures. The dividing lines, which are vertical in the figure and which terminate at *x* and *y*, correspond in their upper parts to the bottom of the calcarine fissures and to the horizontal meridians of both visual fields dividing the upper from the lower extramacular quadrants. In their lower parts (lower in the figure) these lines correspond to the horizontal meridians dividing the upper from the lower macular quadrants. The points where these lines reach the posterior limits of both striate areas (*x* and *y*) correspond to both points of fixation in the visual fields. The vertical lines, or meridians, dividing the left from the right homonymous halves of the macular portion of the visual fields correspond to the posterior (lower in the figure) circumference of the striate areas close to *x* and *y*.

of the macular portion), together with the lower half of the monocular portion of the crossed retina (upper half of the crossed temporal crescent) are projected upon the lower lip of the fissura calcarina (in man, anterior portion of that lip).

(*c*) The projection zone of the monocular temporal crescent occupies the anterior portion of the calcarine striate area, being its most "peripheral" zone (in the monkey in both lips).

(*d*) Homonymous halves of both maculae luteae and of the fovea centralis are projected upon the pole of the occipital lobe, in the monkey behind the ascending and descending branches of the fissura calcarina, and upon the external face of the occipital lobe, the occipital operculum, as far as the striate cortex extends. The upper half of the polar and the opercular striate cortex represents upper quadrants of both homonymous halves of the maculae (lower homonymous quadrants of the macular portion of the visual fields); the lower polar and opercular half represents the lower quadrants of both homonymous halves of the maculae (upper homonymous quadrants of the macular portion of the visual fields). The fovea centralis in particular is projected upon a middle zone stretching across the pole and, in the monkey, across the operculum of the occipital lobe fairly horizontally. In the monkey the foveal projection is probably close to the shallow impression, the external calcarine sulcus or superior occipital sulcus, dividing the operculum occipitale into an upper and a lower half.

(*e*) The horizontal meridian, dividing the upper homonymous extramacular quadrants of both hemiretinae and of the crossed monocular portion and corresponding portions of the visual fields from lower quadrants, extends in a longitudinal sense along the bottom of the fissura calcarina. Its continuation around the occipital pole and, in the monkey, over the occipital operculum approximately toward the midpoint of the sulcus simialis corresponds with the horizontal meridian dividing the upper and lower quadrants of both homonymous hemimaculae. The vertical line dividing both homonymous halves of the visual fields of both eyes and passing through the points of fixation is represented by the posterior boundary of the striate area; in the monkey it stretches in a fairly parallel way along the sulcus simialis. The points of fixation must, therefore, correspond with a central point of that boundary. The dividing line between the macular and extramacular cortex probably has the shape of a sickle with both its horns inclined occipitalward embracing the macular portion of the striate area in front along both ascending and descending branches of the fissura calcarina (in the monkey). Since both horns of the extramacular cortex terminate in sharply extended wedges, the macular cortex in its posterior, and in the monkey in its opercular, portion is not completely surrounded by the extramacular cortex.

9. The bilateral or the double cortical representation of each total macula, with each and all of its receptor elements connected with both hemispheres, has no anatomical foundation. The individual macular elements are represented only in one hemisphere. But each half of each macula is projected upon another hemisphere. In other words, each macular cortex represents homonymous halves of both maculae.

10. The entire striate area receives everywhere afferent visual fibers. There exist no visible gaps (small cortical zones without an afferent fiber supply) which might separate small supplied cortical islets. The number of afferent visual fibers per cortical square unit appears to be larger in the occipital pole and in the occipital operculum than in the calcarine fissure (in the monkey). The coarse exogenous fibers of the visual cortex entering more or less obliquely the lower strata and terminating in the zone of the stripe of Gennari or Vicq d'Azyr,

described by Ramón y Cajal, are afferent visual fibers originating in the external geniculate body of the same hemisphere.

11. The small segments of the visual cortex supplied by individual bundles of the visual radiation have sharp limits and definite but varying triangular form. In different portions of the striate area their shape is different: long narrow triangular strips in the fissura calcarina arranged longitudinally, but more condensed triangles in the occipital operculum and over the occipital pole. The afferent fiber bundles of each of these small cortical triangles are strictly isolated one from another. Each triangle of the visual cortex gets its own bundle independently from the neighboring triangle. There does not, accordingly, exist an overlapping of these small zones, a mingling of their respective bundles, or even a "diffuse" termination of individual bundles of the visual radiation in extensive portions of the visual cortex. Neighboring triangles are supplied by neighboring fascicles of the visual radiation.

12. The entire afferent visual system from its beginning in the peripheral organ (retina) to its termination in the cerebral cortex (striate area) is composed of individual receptor and conductor units. These structural and functional units are strictly arranged according to the "spatial principle" on the one hand, and according to the "principle of neighborhood" on the other. Each area striata is in some sense a faithful copy of both homonymous halves of both retinae. There exists a full preservation of "spatial relations" in the visual cortex as it exists in the retina, though the absolute shape of the "cortical hemiretina" is somewhat changed in consequence of the slight mutual displacement of neighboring units or segments.

13. All visual impulses, whatever their special form or quality may be, and regardless of their ultimate destination, so far as they reach the cortex of the forebrain, first go to the striate area from which they are distributed to other regions of the same and the opposite hemisphere.

14. Since there exists a fixed arrangement of functionally different bundles or segments of the visual radiation (present experiments) as well as of the peripheral portion of the visual system (Rönne, Brouwer-Zeeman), which means a fixed projection of definite retinal quadrants upon definite portions of the visual cortex, symmetrical in both hemispheres, the injuries of the visual system will produce definite symptoms depending on the location and the extent of the injury. Since each of the constituent structures of the afferent visual system and of the visual cortex has its own function, its destruction will be followed by an irreparable and lasting loss of that particular function. The replacement or compensation of the lost function must be achieved by what can be called a more economic utilization of the parts remaining undamaged.

Combining the results of his investigations with those of Brouwer and Zeeman and others, the author has furnished an interesting figure showing the positions of the quadrants of the visual fields in the retina, the external geniculate bodies and the visual cortex, the macular, perimacular and monocular areas being distinguished from each other. Owing to the great number of nerve elements in the macular region of the retina (which are closely packed together there), the number of macular fibers in the optic nerves, the macular area in the external geniculate bodies and the macular portions of the visual area are larger than would be expected from the comparatively small macular area in the retina.

The possibility of lesions in the visual radiation resulting in small central scotomas is explained by the broad but thin form of the macular part of this radiation. Multiple lesions of the vertical macular branch interrupting a great number of individual fibers and finest fascicles will result in no determinable circumscribed loss but in a decrease of the acuity of central vision, as in disseminated sclerosis. The author does not admit that a perfect new functional fovea can be substituted for the old one in case of injury, a claim which tends to disprove his theory of point by point projection. While some degree of compensating function may be assumed by another part of the retina, the high and special organization of the macula would negative a complete substitution. The sparing of the macular field in certain lesions cannot be explained by a complete macular projection on both hemispheres, because this would not account for the cases in which there is no sparing of the macula. Nor can it be explained on the ground of bilateral distribution in the chiasma (because the macula is not spared in complete interruptions of the optic tract) or by means of a partial decussation of the macular portion of the visual radiation (because this is negatived by the author's investigations). The author's explanation of the sparing of the macula lies in the arrangement of this part of the visual radiation. For example, a pathologic process which destroys the anterior portion of the calcarine only and does not injure the subjacent macular radiation will leave the macular fibers and macular cortex undamaged. However, in the case of a tumor which originates from the internal surface of the hemisphere close to the splenium of the corpus callosum, it is likely that the initial extramacular hemianopia will, in the course of the further progress of the lesion, develop into complete hemianopia when pressure interrupts the deeply situated macular fibers. In general, lesions which involve the cortex of the calcarine fissure when pressure is slight or absent (e. g., encephalomalacic and thrombotic lesions) will frequently cause hemianopia, with sparing of macular vision. In short, the author concludes:

> No evidence and no necessity exist for accepting a bilateral cortical representation of each total macula in the sense of Wilbrand, Lenz et al. The preservation of macular vision must be explained by the (1) separate course and protected position of the macular portion of the visual radiation and a well protected location of the human macular cortex, and (2) by the close position of those portions of the striate area which represent extramacular portions of the visual fields, in both lips and in the bottom of the fissura calcarina, which arrangement renders separate injury to those latter regions possible (beside the multiple blood supply of the occipital pole).

The author furnishes an interesting summarization of various possible results from unilateral injuries or pathologic processes which are limited to the occipitoparietal and temporal lobes:

> Unilateral injuries or pathological processes which are limited to the occipitoparietal and temporal lobes, will produce:

(1) A complete homonymous hemianopsia of the opposite side with the vertical dividing line passing exactly through the points of fixation if one entire striate area is destroyed (since the striate area represents an extensive curved surface not lying in one plane this explains why portions of the visual fields so often remain unharmed, especially in gunshot injuries producing a channel more or less straight).

(2) An incomplete homonymous hemianopsia of the opposite side with macular vision preserved if one entire striate area lining the fissura calcarina, except its posterior portion and the occipital pole, is destroyed. The latter can be produced not only by tumors, malacic processes, bleedings, etc., but also by injuries if they are followed by subsequent haemorrhage with destruction of both lips of the fissura calcarina and leave the macular fibers of the visual radiation and the pole of the occipital lobe undamaged. On the other hand, it is easy to understand why gunshot injuries will rarely produce such a form of hemianopsia without infringing in some way or another on a portion of the macular fibers or of the macular cortex. If the position of the gunshot channel is in the horizontal plane, but perpendicular to the long axis of the hemisphere, this will produce either an inferior quadrantic hemianopsia with the preservation of the macula if the upper horizontal branch of the external sagittal layer alone is destroyed, or a rarer superior quadrantic hemianopsia if the inferior horizontal branch alone is interrupted. But it is likely that either the dorsal or the ventral half of the vertical macular branch of the visual radiation will also be damaged, thus completing the hemianoptic loss up to the points of fixation, in the upper or in the lower visual quadrants, depending on whether the lower or the upper half of the perpendicular branch of the radiation is interrupted. If the gunshot channel runs in longitudinal direction but near the median line, it will destroy both lips of the fissura calcarina, while not necessarily destroying the macular fibers. More likely than not the macular cortex will also be damaged in such a case. Yet it is improbable that the macular cortex will be destroyed on one side and be unimpaired on the other. The result will almost surely be an incomplete or complete hemianopsia of the opposite side with perhaps hemianoptic scotomata of the same side.

(3) If only the occipital pole is destroyed this will produce a "central" homonymous hemianopsia of the opposite side. A partial injury of the occipital pole will produce, if the lower half of the occipital pole is destroyed, superior quadrantic macular hemianopsia; if the upper half is destroyed, an inferior quadrantic macular hemianopsia. Small injuries to the macular cortex will produce small congruent homonymous scotomata of the corresponding macular quadrants, usually of an irregular shape.

(4) Partial destructions of the striate cortex in the anterior portion of the fissura calcarina will result in congruent homonymous scotomata of various forms in the perimacular or the "peripheral" portions of visual fields, except when the most oral or also the most "peripheral" zones of the striate cortex along the upper and the lower lip are destroyed; in which case portions of the temporal crescent will be added.

(5) If the fringes of both lips of one fissura calcarina and the bottom of that fissure in its anterior portion are damaged (for example by superficial cortico-malacic and similar processes) there will be an isolated loss of the opposite "temporal crescent." If the bottom of that fissure, besides the fringes of both lips, is also involved in the destruction, including portions closer to the occipital pole, a temporal crescent-hemianopsia will be accompanied by an ordinary hemianopsia of

the extramacular quadrants of both visual fields. It is also easy to understand why loss of vision in the temporal crescent alone is a rare symptom. It is seldom that the anterior portion of the fissura calcarina and its fringes suffer an isolated destruction without impairment of either the visual radiation (at least both horizontal branches), or other more "centrally" located portions of the striate cortex nearer the occipital pole. On the other hand the nearness to the falx cerebri of the anterior portion of the striate area and of the bundles of the visual radiation supplying it (both most dorso-antero-medial and ventro-antero-medial bundles of the horizontal branches first entering into the fissure) can explain the impairment of the temporal crescent as an initial symptom of pathological processes near the splenium of the corpus callosum or even of tumors in distant regions of the hemisphere, e. g., of the frontal lobe, since that part of the visual radiation will be pressed against or pulled onto the posterior margin of the falx and to the tentorium. (There is no need therefore of supposing a "wide" representation of the visual function in the hemisphere.) Later on, when the pressure or pathological process extends into the more caudally situated portions of the striate area and to the visual radiation beneath, incomplete or a complete homonymous hemianopsia will develop.

(6) The peculiar arrangement of the upper and lower "peripheral" segments of the visual radiation, appearing on cross sections through the hemisphere as the upper and lower horizontal branches of the external sagittal layer, with the macular perpendicular branch between them, renders possible a fairly isolated injury of either of the above mentioned branches, followed by loss of the particular extramacular or macular quadrants or of the entire homonymous halves of the fields of vision. Yet the same position of the visual bundles will not readily allow the interruption of both upper and lower horizontal branches of the radiation by a single traumatic injury. For instance, there could hardly occur gunshot injury damaging both of the horizontal branches without some injury to the macular branch. The only possible course of such an injury which would abolish both extramacular quadrants of the visual fields and yet spare macular vision would be a gunshot channel perpendicular to the horizontal plane of the hemisphere and a little away from the falx cerebri yet medially from the plane of the perpendicular branch. (That this would hardly be consistent with the preservation of life is not necessary to point out.) The macular vision will be affected if a gunshot channel has a fairly exact horizontal direction from outside inward, more or less perpendicular to the long axis of the hemisphere, interrupting the perpendicular branch. Since it would probably injure the fissura calcarina itself in its more oral portion there would be at the same time an impairment of the extramacular portions of the visual fields in the form of "peripheral," perhaps multiple, scotomata of various forms, with a portion of the extra-macular visual fields spared. Such a complicated impairment of the visual fields proved indeed puzzling for the "decentralistic" attempts at explanation (see Monakow, 1914, pp. 406, 407).

Lastly, without going into further details of possible combinations of injuries of the central visual apparatus and the various symptoms produced in these ways, it should be mentioned that unilateral symptoms can be combined with bilateral symptoms if the opposite hemisphere is at the same time injured. Since the position of the visual radiation and of the striate areas in the two hemispheres is symmetrical, the injuries, e. g., gunshots which course horizontally and with their direction more or less perpendicular to the long axis of the hemispheres or, what is almost the same thing, to the longitudinal axis of the visual radiation, will produce symptoms, on the whole, of a symmetrical character. If, on the contrary,

the direction of the injury varies from the horizontal plane, different portions of the visual mechanisms will inevitably be damaged on each side and asymmetric symptoms be produced. An almost symmetrical damage to the upper horizontal branches of the visual radiation on both sides owing to a malacic softening can also occur with the resulting incomplete inferior bilateral quadrantic hemianopsia (blindness of the lower halves of both visual fields with the escaping of the macular vision), as one of my unpublished cases demonstrates.

The author further shows that the point by point projection (especially of the macular retina) on the cortex involves central conduction by isolated groups of isodynamic neurons. In this connection I recall a figure by Ramón y Cajal of an external geniculate body impregnated by Golgi's stain which showed in a remarkable way isolated terminal brushes of optic fibers. It may be remarked, however, in the case of two-point and so on tactile discrimination, that Golgi preparations depicted by Ramón y Cajal do not show such segregation in the terminal nuclei of the columns of Goll and Burdach, and that if different combinations are transmitted a cortical discrimination would appear to be possible. The discriminative problems presented by the conduction of impulses arising from movements ("muscle-tendon" sensibility) are of a different nature. It is also pointed out that color stimuli, as well as other visual stimuli, must be received by the striate cortex and not by other cortical areas; that the macular visual cortex serves mostly for the higher psychic processes while the extramacular serves more for reflex acts of the visuomotor apparatus, and that probably the fibers carrying impulses from the homonymous and heteronymous retinas blend, so that in binocular vision there is a single unit for similar visual points from each eye. The latter conclusions are not, of course, proved from observation. There is also a discussion of some points raised by certain investigations of the *Gestalt* psychologists, who claim that the image of an external object is not a mere aggregation or a mosaic of small, independent, individual stimuli coming to a fusion somewhere in the central organ but a "total" psychobiologic phenomenon, a "figure" (*Gestalt*) with a meaning of its own. The legitimate demands of such a psychology the author and I think could be satisfied by integrating association neurons either entirely within the striate area or connecting this area with peristriate areas. It would seem that some of the apparent contradictions arising in experimental work on animal behavior combined with a study of cortical lesions may be due to an insufficient distinction between the reactions to more diffuse or, rather, less analyzed stimuli and those to more discriminative stimuli, and that the progress in certain kinds of reactions which reach their culmination in the human nervous system has as its foundation the presence of a peripheral apparatus which renders discrimination possible and the development of a cortical apparatus which not only synthesizes but is capable of giving

that extensive analysis which would appear to be the basis of concept formation and other psychologic peculiarities which are especially characteristic of human psychology.

It is to be hoped that Dr. Poliak will be able to carry out his difficult program, which has been so well begun. Even the portion completed might be amplified and strengthened by further experimental work along the present lines of research.

OLIVER S. STRONG, PH.D., New York.

News and Comment

THOMAS W. SALMON MEMORIAL

At a meeting of the New York Academy on Jan. 4, 1934, the Thomas W. Salmon Memorial Committee presented to the Academy a portrait of the late Dr. Thomas W. Salmon, which it was stated was intended not as a memorial but rather as "a symbol of a living movement" for mental health. The secretary reported that grants had been made by the committee to aid in various research projects and that the memorial lectures for 1934 will be delivered by Dr. C. Macfie Campbell, professor of psychiatry at Harvard University, at the New York Academy of Medicine on April 13, 20 and 27.

AMERICAN ASSOCIATION ON MENTAL DEFICIENCY

The annual meeting of the American Association on Mental Deficiency, formerly the American Association for the Study of the Feebleminded, will be held at the Hotel Waldorf-Astoria, New York, from Saturday, May 26, to Tuesday, May 29, inclusive.

Abstracts from Current Literature

PARTIAL CORTICAL BLINDNESS WITH PRESERVATION OF COLOR VISION. ISRAEL S. WECHSLER, Arch. Ophth. **9**:957 (June) 1933.

This is the report of a case following carbon monoxide poisoning with asphyxia, and is a consideration of the question of color vision and its cortical localization. It is a fact long established by some clinical observers that various cortical and subcortical lesions may give rise to dissociation of perception of color from visual acuity, and it is well known that in impairment of vision, whether peripheral or central, perception of color is the first to be lost and the last to be regained. These dissociations and the pathologic and psychologic problems to which they give rise, and particularly the question of cerebral localization, have been the subject of extensive, though inconclusive, studies. Leaving out of consideration the rôle which the retinas and the lateral geniculate bodies play in the question of localization, it has been particularly perplexing to determine which part of the cortex is affected in the case of color blindness and whether the lesion causing such loss is cortical or subcortical.

Wechsler's case was that of a boy, aged 13, who in 1929 was overcome by the smoke of a fire. Five members of his family perished, but he, with his father and one sister, survived. He was unconscious for about two hours and was resuscitated by means of a pulmotor. When he revived, he was totally blind and could neither hear nor speak. It was recorded at that time that the pupils were equal and regular and reacted to light, and that both fundi showed recent hemorrhages. Seven months later he had begun to perceive light. He could walk after two months; both hands were in tonic flexion, and he had rhythmic twitchings of the left side of the face with a Babinski sign on the left. For the first five months after admission he had occasional convulsive seizures with attitudes of decerebrate rigidity. A year later neurologic examination showed: The left upper extremity was held in flexion at the elbow and wrist, and there was bilateral loss of association movements in the arms. The patient had some difficulty in the performance of skilled acts, which was due in part to weakness and in part to apraxia. He showed associated movements (reflexes) in one arm on gripping the examiner's hand with the other. There was no incoordination or abnormal involuntary movements. All the deep reflexes were hyperactive; the abdominal reflexes were present, and the Babinski reflex was positive on both sides. The left upper extremity was hypertonic; the other limbs showed normal tonus, while the fingers and toes were hypotonic. There was bilateral pes cavus with some equinovarus. Pain, touch, temperature and vibration were perceived normally throughout, but there was impairment of the sense of position, of two-point discrimination and of stereognostic sense in the fingers of both hands.

The sense of smell was intact. The pupillary reflexes were normally active, the fundi were normal, and there were no ocular palsies, but there was rotatory nystagmus (which, from the history, was definitely congenital).

Examination of the visual powers showed: Perception of form was markedly disturbed. The patient could not recognize small objects, such as a coin, key, pen or watch, and large objects, such as a book, newspaper or telephone, he could distinguish with difficulty. Perception of color, on the other hand, was quick and accurate. He recognized not only all primary colors, but such shades as brown and pink. He knew at once the colors of small objects which he could neither name nor tell the form of. He picked out colors on command. Central vision for colors seemed to be better than peripheral. While it was impossible to outline

the fields of vision, it seemed, by the way he held his head in gazing at an object, that there was some degree of hemianopic defect, and that he used his lower fields in fixation. He groped in trying to grasp objects, and sometimes collided with persons and things, apparently because he could not estimate distance and probably as a result of a defect in visual discrimination of space. There was right supranuclear facial weakness; hearing was normal; the tongue was protruded in the midline; the rest of the cerebral nerves were intact. Speech was unintelligible and dysarthric, but there was no definite evidence either of motor or of sensory aphasia. The patient could write, though he showed some apraxia in the execution of skilled acts, which was, however, difficult to evaluate because of the astereognosis. He showed intellectual deterioration, emotional inadequacy and lack of insight. His mental age, on psychometric examination, was given as 7 years and 8 months, and his intelligence quotient as 52. All the laboratory tests yielded negative results, while the general physical condition of the patient was good.

During the year following admission to the hospital the mental condition improved but slightly; vision returned somewhat, to the extent that he could walk through the wards without colliding.

Judging from the early records and the more recent physical findings, it is probable that the cortex was extensively involved, while the subcortical and basilar structures were less involved. The decerebrate postures which were present early point to lower levels, and the prolonged period of unconsciousness points to a cortical involvement. The loss of hearing can be attributed to temporary bilateral impairment of the temporal lobe. The loss of speech cannot be entirely cortical. The loss of vision is probably cortical, because of the preservation of pupillary reflexes and the subsequent absence of atrophy of the optic nerve, not to mention the disturbances in discrimination of space, the visuopsychic defect and the subsequent relative dissociation in color and light vision. The bilateral hemianopia is probably calcarine. Further cortical involvement may be deduced from the type of sensory loss and the hypotonia of the fingers. The bilateral pyramidal tract signs may be attributed to involvement of the central cortex. The grave mental deterioration points to involvement of the frontal cortex. The loss of associated movements is suggestive of origin in the basal ganglia, as are also the attitude and posture of the feet.

Wechsler has included an extensive review of the literature relative to poisoning with carbon monoxide, with special reference to involvement of the cortex causing mental impairment, but more particularly cortical or subcortical loss of vision and unilateral or bilateral hemianopia. While there are numerous reports of cases in which there was achromatopsia or hemichromatopsia in the presence of good acuity of vision, the reverse, namely, impairment of visual acuity with the preservation of color perception, has not been described except in the case reported by the author.

Abt and Witt described the case of a boy asphyxiated by gas who had loss of vision and preservation of the pupillary reflexes. Brill described color blindness following apoplexy; at autopsy there was softening of the inner surface of the occipital lobe, the cortex bordering on the calcarine fissure, the upper edge of the lingual gyrus and the lower half of the cuneus. MacKay and Dunlop reported a case of partial double hemianopia with permanent complete color blindness, which at autopsy showed lesions in both occipital lobes, in the occipitotemporal lobes and especially in the fusiform lobes. They stressed the fact that the calcarine area was spared and that the white fibers entering it were affected. They cited Verry's case in which hemichromatopsia was caused by a lesion of the white matter of the lingual and fusiform convolutions and the posterior inferior portion of the cuneus. Here also it was pointed out that the cortex was spared. MacKay and Dunlop concluded that color is perceived in the posterior parts of the lingual and fusiform convolutions. Swanzey reported a case of hemichromatopsia, without changes in the fundus, probably cortical in location and apoplectic in origin. Samuelsohn described a case of hemichromatopsia caused by glioma of the optic tract, the thalamus and the geniculate bodies, which spared the cortex.

A fact which points to cortical color representation is the occurrence of fortification scotoma, in which the colors of the spectrum appear as a migrainous aura. Lenz believed that there was no perception of color outside the visual area. Pohlisch also cited cases of amaurosis and loss of color vision in poisoning with coal gas. It will be recalled that Henschen held to the view that there is exact localization in the cortex of the various portions of the retina, the macula also having specific localization. Monakow, on the other hand, contended that the fibers were scattered throughout the geniculate bodies, optic radiation and occipital cortex. Brouwer, compromising, as it were, admitted that the fibers are widely distributed in the geniculate bodies, but that there is some degree of localization; also that while the fibers do go to the occipital poles, they are not exclusively localized there.

There are many references in the literature to mental changes in patients who have survived poisoning with gas. These range from simple defects in memory to complete dementia. Mayer mentioned, among other manifestations, amnestic disturbances. Stengel spoke of manic-depressive and schizophrenic syndromes. Pohlisch also recorded, in addition to amnesias and paraphasias, psychotic syndromes of the manic-depressive and schizophrenic varieties and others characterized by paranoid, confused or catatonic states.

It is always of doubtful validity to draw conclusions as to anatomic localization from clinical findings unsupported by pathologic studies. In this case, bearing in mind the cortical type of occipital blindness, the early loss of hearing, the cortical type of sensory loss, the apparent mental deterioration and the early convulsions, one would be inclined to think that the entire cerebral cortex was affected. The pial engorgement so commonly observed in poisoning with gas and the minute hemorrhages may have been just sufficient to affect the cortex and to spare, in the main, the subcortical structures.

Clinically, there is no doubt that the cortex bore the brunt of the damage. The majority of investigators concur in the view that perception of color probably takes place in the third or fourth layer of the calcarine region, but that memory for colors is a higher psychic elaboration, which takes place on the outer surface of the occipital lobe adjoining the temporal convolutions and the angular gyrus. It is unnecessary to quote the many examples which seem to prove this. That the patient had memory for colors and retained the power of recognizing and naming them shows that just as there can be color agnosia without psychic blindness, the opposite may also be found.

The case reported by Wechsler psychologically is one of a disturbance in symbolic thinking, the greatest difficulty lying in the sphere of higher psychic elaboration, in that the patient suffered from mental or psychic blindness and not from a disturbance in primary retinal perception.

If color vision resides in the cortex and the surface of the brain was destroyed by the pathologic process, color vision should have been lost and not retained. The most probable answer is that either certain parts of the cortex or the layers presumed to perceive and elaborate color vision escaped destruction or they recovered, while the visual areas did not. It is barely possible that there are special color-conducting fibers, but all evidence at hand points to the cortex as the seat of color vision. In any event, the case herein presented warrants the statement that perception of color and visual acuity can be dissociated in such a way that the former is preserved while the latter is impaired. SPAETH, Philadelphia.

THE FORMS OF ASTHENIA. R. BENON, J. belge de neurol. et de psychiat. **32**:727 (Oct.) 1932.

Asthenia may be classified according to degree and according to clinical forms. From the standpoint of degree, Benon describes the light form, or "forme fruste." These patients have been seen and treated by numerous physicians and show a diminution in the capacity for work, which is often accepted with resignation

by the patient. The light forms are noted in the episodic asthenias, in the asthenia of convalescence and in constitutional asthenia. The average or second type of asthenia may manifest itself in a variety of forms, such as episodic, chronic or periodic; it is noted frequently during convalescence from a serious organic disease. The serious or stupor type of asthenia is the extreme degree, and is such that it is impossible for the subject to make voluntary or automatic movements; the patient appears to be completely prostrated, but it can be seen that he is interested in the observer's movements; after recovery these patients may be able to describe the thoughts which occurred during the period of stupor. Such stupor may be observed during infections or intoxications and following traumatism and dementia praecox, and may last for months or years.

From the standpoint of development, Benon describes six types according to development, duration and progress. The episodic, or transitory, asthenias are usually associated with predisposing causes, such as infection or trauma; they are termed secondary because they follow determined causes of nervous exhaustion; they may be accompanied by agitation, with or without hallucinations and with or without mental confusion or delirium. The second type, so-called chronic organic asthenia, includes those forms which accompany any organic malady and appear in direct relation to that infection; ordinarily, chronic organic asthenia is curable if the disease is curable, although there are exceptions to this rule. The third type, or chronic sequela asthenia, follows a physical cause, such as intoxication, traumatism, overwork or emotional disturbance; the condition is usually of average severity and rarely develops into the stuporous type. These patients are said to be made worse easily by irrational therapeutic measures; they are said to find relief by rest only, with a regular life and without excitement; they present a decided tendency toward melancholia or hypochondriasis. The fourth type, chronic associated asthenia, includes those forms which coexist with a determined organic infection, but presumably have no relation to that infection; these cases are most commonly associated with syphilis, but may exist in connection with other organic lesions. The fifth group, or periodic asthenias, includes cases in which the symptoms are present for periods of varying lengths of time; they always end in recovery and have a tendency to recur. The sixth form, or constitutional asthenia, sometimes known as congenital asthenia, is that which is present from birth and manifests itself as soon as the patient is able to demonstrate asthenic symptoms.

Benon differentiates between so-called typical asthenias, which follow some predetermined cause, and the atypical forms, which are usually congential or hereditary. He also groups these asthenic cases according to the symptomatic predominance. Thus, he describes the gastro-intestinal form, in which the symptoms are predominantly those of a gastro-intestinal disturbance; the secondary form, in which there is some disturbance of sensation, and the genital form, which is associated with some disturbance of sexual function. In the fourth type, muscular or psychic symptoms apparently predominate, and the cases manifest either muscular weakness or slowness of cerebration. The cephalalgic form is that in which headache is complained of predominantly. The patients usually complain also of pains in other parts of the body. The insomnious form is that which is associated with difficulty in sleeping—the patients usually go to sleep but wake in the middle of the night and are unable to get further rest. In the hyperthymic form the patients are hyperexcitable and overirritable. The melancholic or hypochondriac form is that in which the patients are particularly anxious about their physical condition. In the pseudoparalytic form the signs and symptoms presented suggest a diagnosis of dementia paralytica. Finally, the form with tachycardia is described. Benon concludes that it is of extreme importance to make a differential diagnosis among the different forms of asthenia because of the difference in prognosis and treatment in these cases.

WAGGONER, Ann Arbor, Mich.

HEMIBALLISM AND THE CORPUS LUYSI. K. VON SANTHA, Ztschr. f. d. ges. Neurol. u. Psychiat. **141**:321 (Aug.) 1932.

Santha reports a case of chronic hemiballism; he recorded a similar case with a lesion in the corpus luysi four years ago. The patient, a woman, aged 57, for a few weeks had had twitchings of the right hand, followed several minutes later by a similar condition in the right leg. The twitchings became more active with time. Examination revealed involuntary movements of the right arm and leg, of a torsion-like nature, involving the entire leg but not the foot, with constant throwing movements of the arm. These movements could be stopped momentarily if the hand was placed flat on the shoulder blade. The movements became more active on voluntary motion. They ceased during sleep. It is noteworthy that the muscles of the neck, head and face took no part in the movements. There was no paralysis, pathologic reflexes, or disturbances of sensibility. For the first two weeks of the illness there was no change in the patient's condition. In the third week there was slight improvement, which continued during the next month.

Necropsy revealed the cerebral cortex studded with senile plaques. There was an area of softening in the left corpus luysi, involving the dorsal part in its medial portion and the dorsomedial part caudally; the pole of the nucleus was uninvolved. Only the caudal part of the field H 2 was destroyed. The nucleus ruber, substantia nigra, thalamus and rubrospinal tract were intact. Histologic examination of the softening in the corpus luysi showed it to be an old lesion.

Hemiballism as a sign of a lesion in the corpus was first signalized by Jakob, in 1923. In 1927, Spatz wrote that this nucleus was the only part of the extrapyramidal system with a circumscribed function. In 1928, on the basis of nine reported cases, Santha concluded that there could be no hemiballism without partial or complete destruction of the corpus luysi. Since then five more cases have been reported. Pelnar and Sikl (1929) reported hemiballism of the left arm, with a small hemorrhage in the right corpus luysi. Balthasar (1930) found a small area of softening in the oral part of the right corpus luysi with hemiballism on the left side; the lesion was circumscribed and limited. Uberall and Samut-Ambrus (1931) found a fresh hemorrhage in the right corpus luysi with hemiballism in the left arm. Nikitius (1932), on the other hand, reported hemiballism of the right side, of seven months' duration, in a patient, aged 77, with an intact corpus luysi; in this case there was a softening in the left lateral thalamic nucleus. Apart from the last case, the evidence seems to show that hemiballism lies in intimate relation to a lesion in the opposite corpus luysi.

Objection to this concept of the corpus luysi is based on two grounds: 1. Some look on the nucleus as a vegetative center for the vasculature and sympathetic innervation of the eye (Kleist) rather than as an efferent motor pathway (Jakob). This vegetative function of the corpus luysi is doubtful. 2. Others believe that the hyperkinesis attributed to the corpus luysi may be produced by lesions of adjacent structures which usually accompany these lesions and point usually to the rubrospinal tract. In the case reported here and in that of the most circumscribed lesion in the literature (Balthasar) the rubrospinal tract was not involved. Furthermore, in cases of the syndrome of the red nucleus the type of involuntary movement is not hemiballism, but is a type of constant tremor which resembles the tremor of multiple sclerosis.

Santha believes with Jakob, Spatz and Balthasar that hemiballism is a syndrome of the corpus luysi sui generis. There has been much controversy as to whether hemiballism is an irritative or an outfall phenomenon. Most people favor the latter theory. The problem of its mechanism is not settled. It is clear, however, that the pyramidal tract must be intact for the production of hemiballism, just as it must be for chorea and athetosis. Balthasar has mentioned cases with a lesion in the corpus luysi, but with another lesion also in the pyramidal tract, in which there was no hemiballism. In this case there was a left hemiplegia with involvement of the right capsule and corpus luysi. In Santha's case there were at no time hemiballistic movements of the head, neck or face. By making serial studies of the lesion it was found that the dorsomedial part was most

affected, and that the oral pole of the corpus luysi was intact. He concludes, therefore, that there were no hemiballistic movements in the head, neck or face because of the intact oral pole, and he believes that there is a somatotopic arrangement in the corpus luysi.

ALPERS, Philadelphia.

ASYMPTOMATIC SYPHILIS. EFFECTS OF VARIOUS DRUGS ON SPIROCHAETA PALLIDA IN THE BRAINS OF RABBITS AND MICE. GEORGE RAIZISS and MARIE SEVERAC, Arch. Dermat. & Syph. **27**:923 (June) 1933.

Although for many reasons the rabbit is a more useful animal than the mouse for experimental research, its utility is severely limited by the fact that spirochetes are, under ordinary conditions, unable to penetrate the central nervous system of the rabbit. Even if the organism is introduced directly into a rabbit's brain it will not persist.

A method of studying syphilitic lesions in rabbits, however, has been worked out by Kolle and Schlossberger. They inoculate emulsified organs of infected mice into the bodies of normal rabbits. In the mouse, syphilis is asymptomatic, but its existence is made clear by its ability to transmit the disease to other animals. The brains of inoculated rabbits show lesions, and the emulsified brains of the infected mice are as virulent as any other organ in that animal. Since the ordinary spirochete will not penetrate the cerebral tissue of the rabbit, it is apparent that by its sojourn in the mouse brain the organism acquires some neurotropic qualities. These characteristics persist in spite of repeated passage through several pairs of animals. The authors intend to use this technic to study the efficacy of various antisyphilitic drugs. Chancrous tissue, excised from a rabbit, is emulsified with sterile saline solution and injected subcutaneously into the back of a mouse. About 0.2 cc. of the semiliquid mass is used. Six weeks or more after the inoculation the brains are removed, minced, emulsified and injected into the testes of normal rabbits. As soon as a testis shows lesions, treatment with the drug being studied is begun. The brain of the treated animal is then removed, minced, emulsified and injected into the testes of a fresh rabbit. If the latter animal shows no lesion, the drug is considered potent.

Arsphenamine, neoarsphenamine, sulpharsphenamine, tryparsamide and acetarsone were used. Apparently all of them are capable of destroying spirochetes in the brain of a rabbit. In the case of sulpharsphenamine and neoarsphenamine, the minimum effective dose could not be calculated, since in each instance the amount used was sufficient to produce sterilization. The minimum therapeutic dose for this procedure, however, is necessarily less than 25 mg. per kilogram for sulpharsphenamine, and less than 50 mg. for neoarsphenamine, since these were the smallest amounts used. With arsphenamine the minimum dosage falls between 10 and 20 mg., the former amount failing to sterilize the brain, the latter succeeding. With tryparsamide larger doses were required than with any of the other four drugs in the group. Three hundred milligrams per kilogram sterilized the brain of one rabbit but had no effect on another. Acetarsone was effective with 125 mg., and appeared gram for gram more potent than tryparsamide.

In the order of their potency, graduated according to the dosage required to sterilize the brain of the rabbit, the drugs could be rated as follows: arsphenamine, sulpharsphenamine, neoarsphenamine, acetarsone and tryparsamide, the last being the least effective.

DAVIDSON, Newark, N. J.

CAPILLAROSCOPY IN PSYCHIATRY. A. MARI, Riv. di pat. nerv. **40**:588 (Nov.-Dec.) 1932.

Mari reviews the status of capillaroscopy as applied in psychiatry and neurology and contributes several hundred observations of his own. The work contains a comprehensive review and summary of the actual status of the subject. For Müller and his pupils capillaroscopy, not limited to the bed of the nail but also at other points of the body, provides nothing more than additional information on

the functioning of the most peripheral vessels. At the most, an atypical capillaroscopic picture may indicate an existing disturbance of the vegetative nervous system. According to Müller, there is no correlation between the mental status and the capillary picture. What is more common is a relation between general endocrine imbalance and an atypical capillaroscopic picture. Another group of investigators, headed by W. Jaensch, attach considerable importance to capillaroscopy; they interpret the changes as an arrest in the development of the vascular system, and because of the common embryologic origin of skin and brain, they infer a possibly abnormal morphology of the brain. Abnormal mental development corresponds to these morphologic abnormalities of the brain.

According to some investigators, a difference in the development of the capillaries occurs in various functional psychoses; in cases of depression, for instance, the capillaries are abnormally large, thus causing a slow blood current, whereas in subjects with manic psychoses the capillaries are narrow, and the flow is supposed to be rapid. According to Hoepfner, in mental deficiency there are peculiar forms of capillary development, and the variation in the caliber of the capillaries goes hand in hand with the periodic variation of the mental reactions.

Mari has worked with more than 490 persons, 150 children and 340 adults; he concludes that there is a higher percentage of abnormal capillary development at the bed of the nail in very severe cases of abnormal development of intelligence, both in adults and in children, in cases of endocrine imbalance, in epilepsy and in other types of cases showing concomitant abnormality of somatic development and particular characters of the skin. He found that in patients with manic-depressive and with dementia praecox psychoses and in other patients whose intelligence is only slightly abnormal there is a lower percentage of abnormal capillaries. On the basis of his findings, he does not accept the view cited, namely, that the abnormal capillary net is an expression of a coexisting arrest of development, particularly in the sense of a morphologic underdevelopment of the brain, because of the common embryologic origin of the skin and the nervous system.

Mari believes that morphologically abnormal capillaries have the value only of pointing out that abnormalities of development may affect capillary districts as well as other somatic ones. The conclusion is that the value of capillaroscopy as a clinical method of investigation is limited. FERRARO, New York.

SUICIDE AS REVENGE. GREGORIO BERMANN, Arch. de méd. leg. **1**:33 (April) 1931.

Bermann, after reviewing several psychologic hypotheses to account for suicide, presents an original interpretation of the act of self-destruction as a form of revenge against some one person or against society as a whole. Esquirol's opinion that only demented persons commit suicide is mentioned and rejected as contrary to statistics. Mejia's theory that suicide is the triumph of social forces over individual will, so that each case promotes the public welfare, is discussed. Much of the confusion is due to the inadequacy of information supplied by relatives and to the inaccuracy of notes left by those who kill themselves. Bermann's hypothesis is based on personal interviews with persons who attempted suicide. Each was studied psychiatrically and sociologically. A series of cases is presented to demonstrate the influence of a desire for revenge against a relative or a lover. One patient killed himself during economic reverses, leaving a note in which he blamed his brother bitterly; a boy killed himself to cause anguish to a brother who had scolded him; a servant, to make an unjust master unhappy, and a lover, to cause remorse to his faithless sweetheart. Adolescent suicides are particularly prone to show this pattern. Children sometimes commit suicide, apparently because of inadequate expressions of love by the parents, actually as an expression of revenge against the indifferent father or mother. Sometimes a racial group is the object of revenge; a case in point is the epidemic of suicides by Japanese on the steps of the American embassy in Tokyo as a protest against the Exclusion Act. A similar instance is that of the anarchist who throws a bomb, destroying himself as well as the objects of his hatred. In this example, suicide expresses vengeance against an economic class.

Most cases of suicide, however, do not demonstrate the revenge motive so directly. The vengeance is directed not against a person or a social group, but rather against the human race as a whole. The person feels inadequate and, consciously or subconsciously, hates the civilization which leaves him with such a feeling. This breeds resentment, which culminates in suicide—an act which is not merely an escape from an inadequate life, but rather a gesture of revenge directed against society.

The paper is concluded by the presentation of a chart used by the department of forensic medicine at Cordova. The chart contains a list of common superficial causes of suicide, which the investigator may check, a paragraph of mental traits permitting the reporter to indicate the temperament of the victim and space for medical, psychologic and sociologic data bearing on the case.

DAVIDSON, Newark, N. J.

PSYCHOLOGICAL WEAPONS IN ANIMAL FIGHT. R. W. G. HINGSTON, Character & Personality **2**:3 (Sept.) 1933.

Hingston's thesis is that animals fight psychologically as well as physically and that this fact "explains in terms of battle everything Darwin included under his hypothesis of Sexual Selection." He makes many interesting observations on animal behavior from which he proceeds to highly questionable generalizations. In such statements as "They do not try to hurt one another, all they want to do is to frighten one another" he assumes the ability of an animal to anticipate the results of its behavior. One wonders to what extent the "threatening behavior" may be described as behavior associated with anger and involving an attitude of preparedness rather than being, as the author claims, "nothing but bluff." The interesting question of how the opponent comes to react appropriately to this initial fight activity is not discussed. There is much that is thought-provoking in Hingston's claim that bright colors are psychologic weapons "intended to strike fear into the mind of the enemy." He disregards completely the conflicting experimental evidence on the question of discrimination of color in animals, as well as the prevalence of pigment in the inorganic world, which must be unsupported by any such excuse for existence. It is probable that animals which are able to distinguish color do react discriminately to situations and to other animals which are characterized, in part, by special colors, but it is doubtful that such a generalization is justified as that color "fulfills the same function in the animal world as does the war-paint employed by the savage." That certain animals react with fear to a display of brightly colored parts is no proof of his thesis. The effect of distribution of long hair on prominent parts as a "threat" is pointed out, but no mention is made of mechanical protective value which in some cases might equally well be argued as of major importance. Courtship behavior is explained as hostile behavior directed toward the rival (present or absent), but why the mate does not react toward this as "threat" behavior is not discussed. Sexual dimorphism is explained by such illogical statements as: "Male has to fight male at the pairing season while female has to fight only with female. Hence males must be better provided than females with threatening colors and fighting-tufts." It would be difficult to agree with the writer that psychologic warfare provides an adequate explanation of the meaning of "colors, adornments, courtships, moults, songs, extravagant weapons, differences between their sexes and other fundamental problems."

MATHER, Howard, R. I.

VERIFICATION OF EMOTIONAL REGRESSION BY TESTS. MANDEL SHERMAN and BLAKE CRIDER, Am. J. Psychiat. **12**:1085 (March) 1933.

The authors present an unusual case of regression, the authenticity of which was verified by objective tests. Their patient was an impulsive, restless married woman, aged 20. She was an adopted child, who had learned of her status as a result of the taunts of her colleagues. She was a difficult child to manage, giving

her parents much trouble because of her constant lying. At the age of 19 she escaped her oppressive home environment by marrying a casual acquaintance. During the first year of married life she engaged in several extramarital affairs, finally deserting her husband. One day she went to sleep at noon and did not awaken until the afternoon of the following day; then, after only a few minutes of consciousness, she fell asleep again. This continued for a week with only occasional and brief waking periods. Shortly after this episode she began to have attacks of regression.

The regressive spells consisted of changes in behavior and personality resulting in the reactions of a child. Asked her age, she would say that she was 6, 3 or 8 years old; in writing, drawing, smiling, talking and acting her behavior during the episode was consistently characteristic of the age level it represented. The girl was originally left-handed, but on entering school had been trained to use the right hand for writing. When she exhibited regression to the 6 year level or younger, she would write with the left hand; otherwise she would use the right hand. She would recall instances of her childhood at the appropriate level, and her descriptions were frequently verified by consultations with observers of that period. The Binet-Simon tests were administered, and the girl always scored the mental age corresponding to the level of regression. The authors found experimentally that an adult unfamiliar with these tests could not on request give answers appropriate to a certain age level. They believe that this consistency of response definitely removes the case from the classification of malingering.

Treatment consisted in discussion of her troubles and of unpleasant childhood experiences and conflicts; she was shown how these difficulties were at the basis of her present attacks; she received semiscientific but accurate books on hysteria and mental hygiene. Her real parents were discovered through the assistance of a newspaper. Within a year after the start of this treatment the patient was apparently normal and well adjusted. The attacks ceased, and the pathologic lying has not recurred.

DAVIDSON, Newark, N. J.

EXCITABILITY OF THE SINGLE FIBER NERVE-MUSCLE COMPLEX. HARRY GRUNDFEST, J. Physiol. **76**:95 (Sept. 16) 1932.

The investigation presented by Grundfest is concerned with the determination of the relation between the intensity of an electric stimulus and the minimum duration for which it must be applied in order to stimulate single nerve and muscle fibers. It was undertaken with the purpose of testing the merits of the conflicting views of Lapicque, and of Lucas and Rushton. The preparation used for the purpose was the single fiber nerve-muscle complex of the retrolingual membrane of the frog Rana pipiens.

The measurements of the strength-duration relationship in the single fiber nerve-muscle complex yield direct evidence of the following facts: Lapicque's law of isochronism is not valid, at least for the system in the retrolingual membranes. The view held by Lucas and by Rushton, which assumes that different excitable substances are present in nerve and in muscle, is in agreement with the results obtained from a study of the single fiber complex.

The present work also yields experimental evidence that the compound curves obtained in the gross preparations are strictly homologous with those obtained for single fibers. The chronaxia of nerve fibers decreases with a decrease in the connective tissue sheath. This conclusion is based on the fact that stimulation of the nerve fiber in the trunk or in a branch produces an increased chronaxia. Because the chronaxia of both muscle and nerve fibers is dependent on the size of the electrode, while that of the nerve also varies with the amount of connective tissue sheath, it seems legitimate to question the further usefulness or significance of Lapicque's concept of "chronaxia." It no longer appears to have the feature of being a simplifying and generally applicable unit of time in the description of the strength-duration curve. Finally, it is concluded that the explanation offered by Moore and Brucke for the heterochronism which has been discovered

in various preparations of nerve and muscle does not seem to have any experimental justification. Their explanation assumes, from analogy with the results for nerve, that a large chronaxia in muscle is due to stimulation of the individual muscle fibers in a locus where the fibers have a small diameter. No such effect of the diameter of the fiber on chronaxia was found, except when the response to direct stimulation of the tip exhibited a latent period of the order of seconds.

ALPERS, Philadelphia.

EXPERIMENTAL SHOCK. R. J. S. McDOWALL, Brit. M. J. **1**:690 (April 22) 1933.

Shock rivals sepsis in its importance in surgical operations. It should be emphasized that shock is not a single entity; it may be produced experimentally and clinically from a variety of causes. Aside from that produced by hemorrhage and cardiac failure, shock may be chemical or nervous. The chemical variety is typified experimentally by histamine shock and clinically by a delayed shock associated with gross destruction of tissue. This variety is enhanced by an anesthetic. The special importance of histamine lies in the fact that it is present in the watery extracts of practically all tissues. The delayed shock of severe burns is probably produced by the absorption of such a substance. It has been shown that histamine acts by dilating the capillaries. As a result, the animal or person bleeds into his own vessels, and with the dilatation of the capillaries they probably become more permeable and the blood plasma rapidly passes into the tissues. This type of shock is enhanced by cold and anesthesia with ether or chloroform. The suprarenal glands probably play an important part in this type of shock. If they are destroyed histamine shock may be caused in unanesthetized carnivora which are otherwise very resistant. Cold exhausts the suprarenal glands; thus, the necessity for keeping a shocked patient warm. The relationship between this type of shock and anesthetics is extremely important, and the author remarks that the person who administers ether or chloroform to a severely damaged patient is guilty of a crime. Nitrous oxide is the anesthetic of choice, since it has been shown that this anesthetic does not render an animal so sensitive to histamine shock as ether. Spinal anesthesia is not a satisfactory substitute because it interferes with the nervous control of the vessels and also causes vasodilatation.

The nervous variety of shock may result from physical damage to the vasomotor center or its efferent paths, from afferent impulses leading to loss of carbon dioxide (acapnia), or from inhibition of the center. The shock dependent on afferent impulses is prevented by deep anesthesia and reduced by morphine. The vasomotor center may be thrown out of action by a loss of carbon dioxide. The chemical and nervous varieties may coexist and enhance each other.

FERGUSON, Niagara Falls, N. Y.

CONCEPT OF PARANOIA DURING THE NINETEENTH CENTURY. F. DA ROCHA, Rev. Assoc. paulista de med. **1**:271 (April) 1932.

Da Rocha finds that the word paranoia, first employed by Hippocrates, reappears in the German medical nomenclature at the beginning of the nineteenth century. Snell, in Germany, and Esquirol, in France, gave the necessary impulse to the study of paranoia, while Morel established a solid basis for the distinction between primary and secondary paranoia. Magnon described separately chronic systematized delirium with progressive evolution in nondegenerated patients and the systematized delirium of the degenerated, which eliminated from the classification the delirium of grandeur of Foville and the delirium of persecution of Lasègue. Schüle, in Germany, accepted Morel's classification, and Mendel described under secondary paranoia what is now known as dementia praecox. Krafft-Ebing, in Austria, adopted the fundamental classification of Schüle and admitted other forms of paranoia, such as the present paraphrenias and the

catatonic, hebephrenic and paranoid dementias. The English authors adhered to the monomanias of Esquirol, qualifying them with suitable adjectives. During the time of the positive school of penal law and criminal anthropology of Lombroso's followers, Tanzi and Riva offered a new explanation of paranoia, claiming that the paranoic patient was a normal person but an anachronism, and consequently lost in a period to which he could not adapt himself. This theory had points of contact with the ideas of Freud on paranoia. Ziehen wanted to call every mental condition paranoia, while Specht wanted to discard the word in favor of the term manic-depressive psychosis. Kräpelin, at the end of the nineteenth century, began by considering mania and melancholia one entity, manic-depressive psychosis. He identified paranoia by defining the disease specifically, and his definition was generally accepted. Etiologically paranoia is a form of mental degeneration which may be inherited. The etiologic factors include alcoholism of the parents and hysteria and various diseases of the parents or of the patient himself during the period of development of his nervous system. Parental syphilis and other forms of degeneration may be contributing causes.

EDITOR'S ABSTRACT.

THE QUESTION OF SENILE PLAQUES. M. N. TOROPOVA, Sovet. psikhonevrol. **9**:79 (Jan.) 1933.

Toropova examined the brains of seventeen patients with senile and presenile psychosis. The evolution of senile plaques is discussed. In the beginning there are foci of condensation of the cytoreticular material, and the fibers crossing these foci become thickened and swollen. The foci are at first amorphous masses, with varied intensity of staining, with granules scattered here and there and with definite swelling of fibers surrounding the foci. These become curved, and the axis-cylinders show a good deal of looping and twisting. In the next stage there is rarefaction of the center, with the formation of empty spaces and the deposition of pigment in the nerve fibers on the periphery. The argentophilic material collects mostly in the center or the periphery, until there appears a classic plaque, with a nucleus, a surrounding "empty corridor" and an argentophilic border. However, the plaque may stop in any stage of development. At times the areas of condensation undergo cystic degeneration, which leads to the formation of status lacunaris. The author has observed how one part of the condensation area led to the formation of plaques, and the other underwent cystic degeneration. Although most investigators maintain that fat is usually absent from senile plaques, Toropova found a good deal of fat in her material; it is present in the glia cells, in the perivascular spaces and in the endothelial cells lining the blood vessels. Sometimes this material collects in big clumps and may be found in the center of the plaques. The author believes that the fat is a secondary but important element in the formation and composition of the plaques. From studying the development of plaques, the author believes that although the plaque starts from condensed and swollen reticula, which are a focal point in the general process of evolution, it incorporates all the various elements which are present at the site of its formation. The author does not agree that the plaques are nothing but an inclusion of a parasitic fungus in the brain, as has been maintained by some German authors.

KASANIN, Howard, R. I .

THE HISTOPATHOLOGY OF FRIEDREICH'S DISEASE: CONSIDERATIONS ON THE PATHWAYS IN THE SPINAL CORD. C. ESTABLE, Trav. du lab. d. recherches biol. de l'Univ. de Madrid **27**:1, 1931-1932.

This article contains a description of the pathologic modifications in the cerebellum, medulla oblongata, spinal cord and spinal ganglia, demonstrated by means of the Cajal and Bielschowsky methods, in a case of Friedreich's disease. The most important conclusions in reference to Friedreich's disease are: Histopathologically, the disease consists in a primary modification of the neurons, chiefly

of the axons; the lesions in the cerebellum are primary, and not a consequence of those in the spinal cord; in the spinal cord the degenerations which are systematic, i. e., localized, affect chiefly the afferent pathways, while in the cerebellum the degenerations affect mainly the efferent paths. None of the lesions can be considered as specific, because they may be found in other diseases and even in traumatic degeneration. In the cerebellar cortex many Purkinje cells are missing; others are not completely developed, although their bodies and dendrites may acquire enormous size; often the axon of the Purkinje cells ceases before it arrives at the white substance, the cells thus becoming cells with short axis cylinders. The baskets and the mossy and climbing fibers also show signs of hypertrophic atrophy, and lose contact with the cells on which they normally end. In the central nuclei the *boutons terminaux* of the afferent fibers often are hypertrophic and have lost contact with the bodies of the nerve cells. This fact, namely, that the contact between fibers and cells may be lost without degeneration of either element, explains the existence of severe symptoms without apparent histologic lesions. Several types of lesions are described in the medulla oblongata, spinal cord and spinal ganglia.

LORENTE DE NÓ, St. Louis.

THE VAGUS INFLUENCES GIVING RISE TO THE PHENOMENA ACCOMPANYING EXPANSION AND COLLAPSE OF THE LUNGS. M. HAMMONDA and W. H. WILSON, J. Physiol. **74**:81 (Jan. 14) 1932.

In this paper the authors consider the function of the nervous influences arising in the lungs which affect the breathing by comparing the results of artificial changes in the pulmonary volume and the changes which occur in the respiratory cycle following section of the vagus nerve. They used a method in which no change in the intrapulmonary pressure takes place, inflation and deflation being produced, respectively, by a negative or positive air pressure acting on the external surface of the body of the animal. A light bellows was used to record the changes in volume in the expired and inspired air. The method, which imitates the natural means by which expansion and collapse of the lungs are brought about, is thought to eliminate any abnormal reflex effects that might be caused for example by changes of pressure within the lungs.

The authors conclude that two influences arise in the lungs which affect the breathing and explain the effects accompanying expansion and collapse of the lungs and the modified rhythm following vagotomy: (*a*) an augmentor influence affecting the frequency and (*b*) an inhibitory influence mainly affecting the depth of breathing, the former being unaffected by changes in volume, the latter increasing with expansion and decreasing with collapse of the lungs. The reflex automatic control of the breathing is confined to the limitation of the depth of inspiration by the inhibitory influence. The function of these two influences, affecting respectively the rate and depth of breathing, is to maintain the most effective ratio between these factors in ventilation.

ALPERS, Philadelphia.

THE DISTRIBUTION OF THE CALLOSAL FIBERS IN THE CEREBRAL CORTEX. J. M. DE VILLAVERDE, Trav. du lab. d. recherches biol. de l'Univ. de Madrid **27**:365, 1931-1932.

The title does not give an exact idea of the content of this important paper, which includes a complete description of the architectonic differences of the following fields of the cerebral cortex of the mouse: area praecentralis granularis, area postcentralis, area infraradiata, area praecentralis agranularis, area peristriata, area retrosplenialis agranularis and area retrosplenialis granularis, names which correspond with those given by Rose. A happy combination of Cajal's reduced silver methods with the embryologic method of Flechsig has enabled Villaverde to differentiate the projection and association systems of these fields. The different systems of fibers develop, not simultaneously, but according to a definite order. If Cajal's method is used at different stages of development, it is possible to secure

stains in which the individual systems may be identified. The fibrillar systems and the plexuses they form in the different layers of the cortical fields mentioned are described minutely.

With reference to the callosal systems, the main conclusion is that the area praecentralis granularis and the area praecentralis agranularis have two systems of callosal fibers, a homotopic system, constituted by fibers arriving from the same fields on the other hemisphere, and a heterotopic system arriving from other fields on the other hemisphere, and that the callosal fibers, after having given some collaterals in the deep layers, end in the superficial ones.

LORENTE DE NÓ, St. Louis.

TRAINING THE HIGH GRADE MENTAL DEFECTIVE FOR COMMUNITY LIFE. SANGER BROWN, JR., Ment. Hyg. **16**:440 (July) 1932.

For the purposes of the article, Brown defines high grade mental defectives as borderline types and morons whose intelligence quotients fall into the range between 65 and 79. These children on parole often fail seriously in their efforts to make social adjustment, in spite of what appears to be excellent institutional training. The first cause for the failure is the poverty of opportunity for social training which is inevitably the lot of a child surrounded by mentally defective children. This points the way to a method for remedying the fault, namely, intelligent social training. Mental defectives of the higher grade should be housed in separate quarters; infants should be placed in a well equipped and intelligently manned nursery school, while somewhat older children should attend an institutional kindergarten. The older children should be housed in cottages under the supervision of trained nurses. They should be sent to the regular community schools, away from the grounds of the institution. It may be necessary to modify the curriculum or even to provide separate classes, but the school building they use should be part of the community's public school system, and not part of the general training school for the feebleminded. When possible, boarding homes under general institutional supervision should be established, so that these children may live in the atmosphere of a home and take part in the church, school, recreational and other social activities of the ordinary community routine. Only in this manner will it be possible to overcome the serious limitations inherent in institutional life as a training for social responsibilities. DAVIDSON, Newark, N. J.

FURTHER EXPERIMENTS UPON THE DEVELOPMENT OF SPINAL GANGLIA IN AMBLYSTOMA. S. R. DETWILER, J. Comp. Neurol. **54**:173 (Feb.) 1932.

Previous studies of the author on young amphibian embryos have shown that there is a developmental functional relationship between skin area, muscle mass and spinal ganglion cell proliferation. The question at issue here is whether early stages of myotomes or their antecedent unsegmented mesoderm can influence the segmentation and differentiation of spinal ganglia. The experiments include previous ones as well as new ones with a greater range of conditions.

The author observes that extirpation of somites or presomite axial mesoderm in Amblystoma is followed by marked disturbances in the development of the spinal ganglia. The orderly segmentation of the crest cells according to the original somite boundaries fails. Despite the absence of muscle and axial cartilage, irregularly or incompletely segmented ganglia may develop. The ganglia which do develop in the absence of somite tissue are usually much smaller than normal, are usually reduced in number and show less differentiation. When a supernumerary piece of spinal cord, divested of mesoderm, is grafted lateral to the host's somites, irregular ganglia may develop between the donor cord and the lateral boundaries of the host's myotomes. Such ganglia may undergo considerable differentiation.

The results suggest to the author that ganglionic neuroblasts are capable of a certain amount of self-differentiation in spite of the fact that normally they are markedly influenced by the developing somites and axial cartilage.

ADDISON, Philadelphia.

PARANOID REACTION OCCURRING IN WOMEN OF MIDDLE AGE. G. H. STEVENSON and S. R. MONTGOMERY, Am. J. Psychiat. **11**:911 (March) 1932.

The persistence of a clinical feature in a group of patients with similar psychotic pictures suggests a common underlying cause. Paranoid trends constitute such a factor, and this symptom may be found in almost any psychosis; in a peculiar form, however, it is a characteristic of psychoses of the involutionary period. The authors do not consider the freudian interpretation of this delusion universally valid, finding that a fear of guilt and a projection of this fear offer a more acceptable explanation of the paranoid trend than the homosexual or narcissistic hypothesis presented by psychoanalysts. Their study consists of an examination of 11 women, all married and ranging in age from 42 to 65; all but 2 of the patients were in the forties. All voiced persecutory delusions and little else. In each instance the onset was very gradual; personality was well preserved, and physical health was good. The women were all respected members of the community and of unreproachable moral integrity. None of the patients recovered. In most cases the delusion referred to persecution by the husband.

The authors found a common environmental factor in the histories of all the patients, that is, a real or an imaginary overt act contrary to the ethical principles of the patient. Instead of dealing with this by prayer or repentance, the subject quieted her conscience by projecting the guilt outward. The desire to be punished for her sin was likewise projected and slowly evolved to the state of a persecutory delusion.

DAVIDSON, Newark, N. J.

A CASE OF CHRONIC TETANY. DESMOND CURRAN and L. C. COOK, Lancet **2**: 735 (Oct. 1) 1932.

A woman, aged 40, was admitted to a state hospital because of an illness of five years' duration. There was a history of domestic worries at the time of the onset of the condition, which seemed to be an adequate psychogenic factor. About once a month just before menstruation she suffered a "squeezing" pain in the epigastrium followed by shivering and diarrhea. This lasted for a few days and was followed by a black appearance of the fingers, which became cold and cramped. These cramps at times were associated with twitching of the muscles of the face and elbow, which would last for two or three days. There were concomitant insomnia and depression. Gradually she became more disinterested and the depression deepened. Physically she showed the results of having had rickets when a child. She was of small stature and poorly nourished, evidencing recent loss of weight. There were bilateral opacities of the lens.

In an attack she showed the classic signs of tetany. The serum calcium was 6.5 mg. per hundred cubic centimeters; the plasma inorganic phosphorus, 3.1 mg. With calcium therapy the improvement was marked, with accompanying increase of the blood calcium and phosphorus.

The depressed reaction and behavior had masked the true condition during frequent visits to a psychiatric outpatient clinic and only a purely functional disorder had been considered before admission to the hospital.

BECK, Buffalo.

CUTANEOUS TACTILE LOCALIZATION. E. A. BLAKE PRITCHARD, Brain **45**:350 (Sept.) 1931.

Pritchard reviews previous theories in regard to the supposed pathway for cutaneous localization and the localization of touch. The view is presented that the function of what is generally called the sense of touch is localization; accurate localization apart from touch exists not as a sensory impression, but only as a theoretical concept. From three experiments it is inferred that: (1) Accurate localization of cutaneous stimulation is possible when the sensibility to touch is present, and is in abeyance when this form of sensibility is absent; (2) localization shares with sensibility to touch its independence of variations in the strength of the stimulus, and (3) it is only when the application of the stimulus used involves mechanical deformation of the skin that accurate localization is possible.

Accuracy of localization characterizes tactile responses in creatures of most advanced neural development. Tactile space perception is developed through the characteristic exteriorization of mechanically aroused impressions. The significance of tactile space perception is overshadowed by that of visual space perception, and both touch and vision are completely exteriorized. Not only is tactile space perception necessary for the coordination and adjustment of movements, but only accuracy in the execution and assessment of movements makes the development of tactile space perception possible.

MICHAELS, Boston.

TRAUMATIC SYNDROME OF THE PETROBASILAR SUTURE. J. ROLLET, Rev. d'oto-neuro-opht. **10**:658 (Nov.) 1932.

The rare syndrome of the petrobasilar suture is characterized by paralysis of the external motor oculi nerve, the syndrome of the posterior lacerated foramen and a lesion of the inferior petrosal sinus. Such a case was that of a man who, following a fall, presented paralysis of the right sixth nerve and of the right superior constrictor muscle; hypesthesia of the right half of the pharynx; diminution of the gagging reflex; paralysis of the right vocal cord (cadaveric position) and of the right sternocleidomastoid and trapezius muscles, and paralysis and hypesthesia of the right half of the palate. There were dysphagia on swallowing solids and later regurgitation of liquids through the nose. The pulse rate varied between 120 and 80 per minute. A roentgenogram revealed blurring of the outlines of the posterior lacerated foramen and clouding in front of the foramen extending to the point of the petrous process but not involving the foramina containing the branches of the fifth nerve. Hemorrhagic spinal fluid was obtained. It is probable that the shadow was due to a hematoma from rupture of the inferior petrosal sinus. Often, in this condition, only the ocular lesions have been correctly interpreted and referred to a lesion at the petrous apex; disturbances of deglutition and cardiac rhythm have been attributed to meningeal lesions, and the spinal paralysis has been considered as a direct contusion of the shoulder.

DENNIS, Colorado Springs, Colo.

TWO CASES OF OLIGODENDROGLIOMA: WITH REMARKS ON THE GENERAL CLINICAL FEATURES OF SUCH CASES. J. PURDON, Brain **54**:330 (Sept.) 1931.

The cases described are the only ones encountered at the National Hospital during the last ten years. With previous clinical accounts of other authors there are nineteen cases for discussion. Oligodendrogliomas have a tendency to lie laterally (sixteen cases), and in the frontal and parietal lobes; in three cases the tumor lay across the middle line of the brain and was clinically atypical. In 84 per cent of the cases the symptoms began between the ages of 23 and 45. The average period between the first symptom and operation (or death) in the sixteen lateralized tumors was nearly five years. In general, "deficiency" symptoms of any severity were absent from all the fully recorded cases, but "irritative" phenomena were frequent. In one third of the tumors of the hemispheres, headache seemed to be the first symptom. The roentgen appearance is almost pathognomonic of an oligodendroglioma of the lateral group. The growths do not have a tendency to infiltrate at all widely, but they are large masses of irregular outline. They are of very slow growth, and calcification is evidence of an extremely chronic degenerative process. In many instances the tumor probably begins to grow in early adult life; however, the growths are relatively favorable for palliative operation.

MICHAELS, Boston.

AMYOTROPHIC LATERAL SCLEROSIS WITH NYSTAGMUS. BOISSEAU and BRISSAUD, Rev. d'oto-neuro-opht. **10**:257 (April) 1932.

A man, aged 24, presented himself with flexion of the head forward, swinging arms and spasmodic gait. The family history was without significance. He had

had measles and an attack of appendicitis at the age of 20. The present illness began at the age of 19½ with awkward movements; six months later there was fever which lasted ten days. Examination revealed atrophy involving the thenar and hypothenar eminences, the interosseous and lumbrical muscles, and the muscles of the forearm, of the region around the mouth, and of the tongue and palate. There was a spastic paraplegia which caused a spastic gait and falling, accompanied by painful cramps. Fibrillary contractions were marked, and all reflexes except the cutaneous were increased. The Wassermann test of the blood was negative. In the extreme lateral position of the eyes, nystagmic jerks were clear. A caloric test revealed normal labyrinthine reactions. The notable points in this case are: (1) the youth of the patient, (2) the long duration of the disease and (3) the nystagmus. Nystagmus in amyotrophic lateral sclerosis is rare. Van Bogaert said that ocular and vestibular disturbances may exist, but he did not observe nystagmus in his thirty-eight cases. Barré has reported a case, and Barré and Metzger saw two patients. DENNIS, Colorado Springs, Colo.

INTERRUPTION OF THE CATATONIC SYNDROME. S. GULLOTTA, Riv. di pat. nerv. **40**:241 (July-Aug.) 1932.

Following the work of Lorenz and his associates with sodium amytal, the author has treated twelve catatonic patients, some of whom did not have dementia praecox, in order to interrupt the catatonia, a process which the author calls decatatonization. He concludes his investigation by stating that of all the methods of decatatonization, the one employing narcotics of the barbituric series is the most effective, and that the practice of decatatonization is valuable in the examination and diagnosis of catatonic patients. Because of the fact that catatonia can be reproduced through sleep and the use of hypnotics and can be interrupted by abrupt awakening, and because of the extraordinary resemblance of the biologic reactions of sleep and catatonia, it is supposed that a connection must exist between the two phenomena. These facts also confirm, according to the author, the conception that catatonia depends on physiologic modifications of the nervous system. The decatatonizing substances are mainly hypnotics which act on the subcortical centers. They probably induce physiochemical changes which are translated into a return of function to or a stimulation of the centers that were previously inhibited or intoxicated and into a reestablished equilibrium between them and the cerebral cortex. FERRARO, New York.

EXPERIMENTAL STUDIES ON IMMUNITY IN DEMENTIA PARALYTICA. A. GALLINEK, Monatschr. f. Psychiat. u. Neurol. **79**:392 (July) 1931.

In syphilis, antibodies are formed which act as a defense against the spirochetes. This defense mechanism appears weakened in dementia paralytica. Thus, dark-field observations showed that the serum of normal persons as well as the serum of untreated patients with dementia paralytica killed the spirochetes of syphilis in from five to six hours. On the other hand, the organisms were destroyed in about seventy-five minutes by the serum of untreated patients showing early secondary manifestations, and in from twenty to thirty minutes by that of patients with cerebrospinal syphilis. The results obtained in tabes were not uniform, the duration of life of the spirochetes varying from thirty minutes to eight hours. The effect of malarial treatment in dementia paralytica was also investigated. During the course of the treatment, and immediately afterward, the spirocheticidal activity of the serum was unchanged. Six months later the serum from these patients killed the organisms in two hours. Cases studied a year and a half after malarial treatment yielded results similar to those obtained in untreated patients. The author concludes that the therapeutic use of malaria in dementia paralytica apparently leads to an increase in the defensive power of the organism which reaches its maximum in six months. ROTHSCHILD, Foxborough, Mass.

A Study of the Eye Findings in a Group of Epileptics with Reference to the Mechanical Theory of Epilepsy. Harry Costeff, Am. J. Psychiat. **11**:747 (Jan.) 1932.

On the hypothesis that a long continued increase in intracranial pressure would manifest itself in pathologic conditions within the eye, Costeff undertook to study the eyegrounds of epileptic patients to determine the frequency, constancy, persistence and significance of changes in the fundi of these patients. His group consisted of 114 epileptic persons ranging in age from 17 to 77. In 9 of the cases the fundi could not be visualized; in the remaining cases, normal eyegrounds were found in 46 cases, or 47 per cent. In more than half the cases, therefore, an abnormality was found. There were 32 instances of hyperemia of the fundus, 17 of optic atrophy and 11 of choroiditis. In the 59 patients who presented ocular disease, the condition seemed permanent in 45. The fact that so large a group exhibited an identical pathologic condition (passive hyperemia) is significant. Costeff considers the existence of passive hyperemia as evidence of increased intracranial pressure: he reasons that in the eyeground there must be an equilibrium between the venous pressure and the pressure of the surrounding fluid medium—the cerebrospinal fluid. Consquently an increase in the pressure of the latter will be met by compensatory changes in the retinal vessels. His work tends to support the hydraulic theory of the cause of epilepsy.

Davidson, Newark, N. J.

Lesions of the Cerebellum in Mongolian Idiocy, and Some Considerations on the Pathology of the Cerebellum. J. M. de Villaverde, Trav. du lab. d. recherches biol. de l'Univ. de Madrid **27**:111, 1931-1932.

This article is a description of the lesions demonstrated with the Cajal and Bielschowsky reduced silver methods in a case of mongolian idiocy. The lesions are not characteristic; a great number of Purkinje cells are missing, the remaining ones being generally arranged in groups of a few, separated by empty spaces. Often the cells show clear symptoms of degeneration. The baskets on the Purkinje cells generally are constituted by a small number of fibers, which are thicker than normal. Villaverde emphasizes that a basket has never been found without a cell in it, although on many occasions the fibers of the baskets are not in contact with the cell bodies, and that the opposite may be true, i. e., that Purkinje cells exist without the corresponding basket. The climbing fibers often show degenerations. Villaverde rejects the theory that explains mongolian idiocy as a regression to an older phylogenetic type; he thinks rather of alterations in the endocrine metabolism which determine an incomplete development of the nervous system.

Lorente de Nó, St. Louis.

The Nature of the Human Factor in Infantile Paralysis. George Draper, Am. J. M. Sc. **184**:111 (July) 1932.

The author stresses the fact that the type of human being, in addition to the specific virus of meningitis or poliomyelitis, is an essential etiologic factor. In the 1916 epidemic of infantile paralysis, a description of definite morphologic characteristics in the type of child was given: a well grown, plump child with a history of difficult dentition; among the adolescents, a more delicate type, composed of brunettes with crowding of the teeth. In the recent epidemic, more technical methods were employed; the broad, wide-eyed expression in children was again noted. The one outstanding measurable character is the biiliac-biacromial diameter ratio, in which the pelvis is wide as compared with the shoulders. The subjects with infantile paralysis possess nail lunulae much less often than those of the control series, but the epicanthal fold and pigmented spots occur more often in the group with infantile paralysis. Spacing of the teeth is commonly found, with failure of eruption and irregularities. The general picture in the afflicted persons usually suggests status lymphaticus, indicating deficiencies of the hypophysis,

gonads and suprarenal cortex. In the development of paralysis in the occurrence of infantile paralysis, the constitution of the child is of greater significance than the virus.

MICHAELS, Boston.

TREATMENT OF TETANUS. LESLIE COLE, Brit. M. J. **1**:743 (April 23) 1932.

The author reports clinical findings and the treatment in ten cases of tetanus, five of which resulted in recovery. He emphasizes the fact that tetanus is still sufficiently common in some districts to warrant reasserting the importance of prophylactic antitoxin after even trivial wounds. Superficial healing and formation of a scab over a trivial wound may create a cavity for anaerobes to grow in. In regard to the prognosis, the following seemed significant. A long incubation period increases the chance of recovery. Slow onset of symptoms is a favorable sign. Old age and a severe wound, which cannot be thoroughly drained, tend to make for an unfavorable issue. Pain and stiffness in the back of the neck and spine may be the earliest symptoms. These, associated with a slight stiffness of the jaw and rigidity of the abdomen, should suggest tetanus. Treatment should begin as early as possible. The local wound should be thoroughly cleaned and drained at the earliest moment. Antitoxin should be given as soon as possible in very large doses, preferably by the intravenous route. Spasms and pain should be relieved. For this purpose, the author suggests that avertin may prove of value. Dextrose should be given freely and the nourishment maintained.

FERGUSON, Niagara Falls, N. Y.

CONCOMITANT CONVERGENT STRABISMUS IN A SUBJECT WITH UNILATERAL HYPERMETROPIA, SUPERVENING AFTER INTERNAL OPHTHALMOPLEGIA IN DIPHTHERIA. JEAN SÉDAN, Rev. d'oto-neuro-opht. **10**:404 (June) 1932.

The subject of this report is a patient, aged 12, who in May, 1931, had a sore throat, without a febrile reaction. The cause was not determined until twenty days after the onset. Only after energetic serum therapy lasting seventy days, during which 400 cc. of serum was used, did the cultures become negative. Sédan had had this child under observation from the age of 5, when it was determined that the right eye was emmetropic and the left eye hypermetropic (3.5 diopters) and slightly amblyopic. The globes were parallel. Total correction was tolerated only after glasses had been worn for several years. In October, 1931, the patient began to squint, and it was learned that during the preceding summer he had had paralysis of accommodation. Examination revealed a diminution of vision to 6/10 and marked concomitant strabismus in the left eye. According to Onfray, strabismus often occurs with infectious diseases, such as whooping cough, the eruptive fevers and diphtheria; the last condition is frequently followed by ocular paralyses. Worth supposed that debilitating illnesses are followed by paralysis of accommodation, and Onfray thought that certain acute diseases may be occasional causes of strabismus.

DENNIS, Colorado Springs.

EXPERIMENTS ON THE FUNCTION OF THE LATERAL LINE ORGANS IN THE LARVAE OF AMBLYSTOMA PUNCTATUM. ERNST SCHARRER, J. Exper. Zool. **61**:109 (Jan. 5) 1932.

To eliminate visual stimulation, the anlagen of the eyes were removed in larvae of Amblystoma punctatum in stage 35 (Harrison). When the larvae had reached the feeding stage, they were tested. They reacted with a snapping reflex to minute streams of water directed toward the side of the head. They also snapped at streams directed against the flank. In another series the eyes and lateral line organs of one side of the head were removed in the late tail-bud stage. On being tested when they had reached the feeding stage, they reacted by snapping only when the stimulus was applied to the side which had not been operated on. The snapping reaction indicates that the lateral line organs may play an important rôle in the obtaining of food. Larvae in which the anlagen of

the nose and eyes were removed in early stages without injuring the lateral line organs quickly captured living Enchytraeus, which by their movements caused irregular streams in the water. The larvae located the worms at a distance of nearly half a centimeter. Vibrations of the water appeared to have more attraction for a blinded Amblystoma larva than the chemical stimulus from a crushed piece of worm.

WYMAN, Boston.

THE ABSENCE OF PAINFUL SENSATION IN THE CAT DURING STIMULATION OF THE SPINAL ACCESSORY NERVE. WILLIAM F. WINDLE and L. C. DELOZIER, J. Comp. Neurol. **54**:97 (Feb.) 1932.

It is well established that the spinal accessory is a mixed nerve. The function of the sensory neurons is unknown. The present experiment was made to determine whether or not pain was carried by some of the neurons. Fifteen cats were used. With the animal under light anesthesia, the spinal accessory nerve was dissected in the neck for about ½ inch (1.2 cm.) central to the place where it enters the sternocleidomastoid muscle. A shielded bipolar electrode was placed on the nerve, and the animal was allowed to recover from the anesthetic. Faradic stimulation was applied. Weak stimulation of the intact nerve resulted in pain reactions, which, however, were not so marked as those following stimulation of the cutaneous nerves of the neck. After section of the nerve at the muscle, weak stimulation produced no results and that of maximum strength was followed by responses in only one of the animals tested. The author concludes that the sensory neurons of the spinal accessory nerve ordinarily do not conduct painful afferent impulses, and suggests that they are probably proprioceptive in function.

FRASER, Philadelphia.

GROWTH ACCELERATION AND REGULATION IN HETEROPLASTIC SPINAL-CORD GRAFTS. S. R. DETWILER, J. Exper. Zool. **61**:245 (Feb. 5) 1932.

When the brachial region of the spinal cord in embryos of Amblystoma tigrinum is substituted for the corresponding region in embryos of Amblystoma punctatum, the graft, in early stages of larval life, grows with a velocity that is greater than that exhibited by either the tigrinum donor control cord or the punctatum control cord. This differential growth rate is not obliterated under conditions providing for maximal feeding on the part of both host and donor control larvae. Regulatory processes play an important part in later growth. From thirty to thirty-two days after the operation, the graft in the punctatum host is smaller than the donor control homolog, regardless of the nutrient level of the donor control animals, and from this period on it is regulated to the size normally attained by the corresponding region in a normal punctatum cord. It is apparent that the acceleration in the early growth of the graft over both donor control and host control homologous regions cannot be explained alone on the basis of growth depending on food intake. The true nature of other accelerator and also regulatory influences remains obscure.

WYMAN, Boston.

ROENTGENOLOGIC DIAGNOSIS OF TUMORS OF THE THIRD VENTRICLE. K. ALBRECHT, Monatschr. f. Psychiat. u. Neurol. **79**:136 (June) 1931.

Albrecht reports a number of cases in which a diagnosis of tumor of the third ventricle was made by means of ventriculograms. Lateral exposures of the skull were studied. Under normal circumstances the third ventricle does not hold sufficient air to be well defined in lateral views. In cases of hydrocephalus due to atrophy of the brain it becomes symmetrically enlarged, appearing similar in shape to a segment of an orange with the convex side upward. Hydrocephalus produced by occlusion leads to enlargement which is greatest at the thinnest parts of the ventricular walls, that is, anteriorly where the wall is formed by the lamina terminalis and posteriorly in the region of the recessus infundibuli. If a tumor is present in the third ventricle, the shape of the ventricle may be altered, and

the outline of the tumor may be seen encroaching on the lumen. In order to obtain satisfactory plates it was necessary to remove more than 50 per cent of the ventricular fluid. With the patient's head placed laterally, fluid from the upper ventricle was removed and replaced with air until air could be aspirated from the opposite lateral ventricle. In this manner proper filling of the third ventricle was assured.

ROTHSCHILD, Foxborough, Mass.

FUNCTIONAL APHONIA: SOME OBSERVATIONS ON ITS CLINICAL ASPECTS. F. DOUGLAS MARSH, Lancet **2**:289 (Aug. 6) 1932.

Functional aphonia is an inability to produce the voice owing to failure of the neuromuscular apparatus in the absence of organic disease. A summary of sixteen cases shows that functional aphonia may be associated with sepsis in the upper air passages. Functional aphonia has been synonymous with hysterical aphonia. The author suggests that it is advisable to classify functional aphonia into two classes, primary and secondary. The primary class is exemplified by the purely hysterical forms, and the secondary class by the forms that start with laryngitis secondary to a septic focus in the upper air passages. The series of cases reported shows clearly that a determining cause is often present. When found, it should be treated and should be regarded as no less important than the restoration of the voice. There is seldom any difficulty in obtaining complete restoration of the voice by electrical stimulation, by suggestion or by instruction in proper voice production. This, with proper handling of the septic focus, will do much to prevent relapse, which otherwise is apt to be frequent.

BECK, Buffalo.

THE HISTOLOGY OF POSTERIOR REGENERATION IN THE POLYCHAETE CHAETOPTERUS VARIOPEDATUS. G. H. FAULKNER, J. Morphol. **53**:23 (March 5) 1932.

After amputation, the wound is closed by the protrusion and lateral expansion of the alimentary canal over the cut muscles and its fusion with the epidermis laterally. Associated with this expansion is a divergence of the two adjacent halves of the ventral nerve cord in the last remaining segment. The whole of the new regenerated lobe is thus interneural, being an enlargement of the small area separating the two nerve cords. Neuroblasts are normally located interneurally, and during regeneration these proliferate and migrate throughout the new lobe. At first the neoblastic mesenchyme filling the lobe is homogeneous, but later cells settle down against the outer wall forming the new epidermis. Internally the mass acquires paired cavities, and the cells surrounding these cavities differentiate into muscle, peritoneum, etc. Thus one type of cell gives rise to the whole of the regenerated papilla. These cells are also the mother cells of the gametocytes.

WYMAN, Boston.

EXPERIMENTAL STUDIES ON THE EFFECT OF SECTION OF THE VAGUS NERVE ON GASTRIC SECRETION. JULIUS FRIEDENWALD and MAURICE FELDMAN, Arch. Int. Med. **49**:234 (Feb.) 1932.

To determine the effect of section of the vagus nerve on the secretion of gastric juice, Friedenwald and Feldman studied this function in dogs. Alcohol was introduced into the stomach through a tube, and the contents of the stomach were removed forty minutes later. Into other animals 1.5 mg. of histamine was injected subcutaneously, the gastric contents being removed half an hour later. After the normal findings were established, the vagus nerve was sectioned, and gastric analysis was again performed. The findings were the same after the right vagus nerve was cut as before the operation; little change followed injury to the left vagus nerve trunk just below the diaphragm, but in many dogs section of the anterior gastric branch of the left vagus was followed by marked hypochlorhydria. The experiments led the authors to believe that changes in gastric secretion following injury to the vagus nerve are inconstant and usually moderate.

DAVIDSON, Newark, N. J.

REMARKS ON THE TREATMENT OF TETANUS, DIPHTHERIA AND OTHER NEUROTROPHIC DISEASES BY THE METHOD OF PHYLAXIS. RENÉ CRUCHET, Brit. M. J. **1**:85 (Jan. 16) 1932.

As early as 1847, it was shown by Eschallier that inhalations of chloroform had a beneficial effect in the treatment of tetanus. Others of the French school used this and other drugs, although for some reason the author does not think that this principle of treating neurotropic diseases has commanded the attention it deserves. The theory of its effectiveness is that such drugs as chloroform impregnate the lipoids of the nervous system in such a way as to render it impossible for the toxins having a neurotropic affinity to become fixed. The author reports success in tetanus and diphtheria by a combination of chloroform anesthesia and injections of antitoxin, and suggests that it might be of value in all neurotropic diseases, such as are produced by influenza, typhoid fever, herpes zoster, varicella, typhus and epidemic encephalitis, and in poisoning by strychnine, phalline, snake bite, the botulinus bacillus, curare, etc.

FERGUSON, Niagara Falls, N. Y.

THE RELATION OF THE SYMPATHETIC NERVOUS SYSTEM AND GENERALIZED LYMPHOID HYPERPLASIA TO THE PATHOGENESIS OF EXOPHTHALMIC GOITER AND CHRONIC LYMPHATIC LEUKEMIA. HARRY B. FRIEDGOOD, Am. J. M. Sc. **188**:841 (June) 1932.

The author attempts to show clinically and pathologically that the difference between exophthalmic goiter and chronic lymphatic leukemia is essentially quantitative, the lymphoid and splenic lesions being much less extensive in the former. It is difficult to follow the argument, which is interesting, when a fundamental disorder common to both is suggested by the fact that both respond to compound solution of iodine. The hyperactivity of the sympathetic nervous system (for which iodine has a "selective sedative action") is mentioned as having paramount importance in their pathogenesis. The theory of hyperthyroidism secondary to and dependent on hyperplasia of the thyroid gland is not entirely adequate to explain exophthalmic goiter.

MICHAELS, Boston.

INTRAMUSCULAR LIVER EXTRACT THERAPY IN THE TREATMENT OF PERNICIOUS ANAEMIA. L. S. P. DAVIDSON, Brit. M. J. **1**:269 (Feb. 13) 1932.

The author reports his experience with the intramuscular injection of a liver extract. The reason for its use in preference to the oral administration of liver is that in effectiveness it is about a hundred times that of raw liver given by mouth. It is of particular value in cases of pernicious anemia in which the patients are critically ill, with marked nausea and vomiting, and in the more extreme cases transfusion of blood can usually be avoided. The so-called liver-resistant patients should be treated by intramuscular injection of this extract. In patients in remission, fortnightly injection of liver extract enables the maintenance dose of liver to be reduced to limits which can easily be tolerated. Attention is called to the fact that a low blood level seems to be responsible for the changes in the cord, and thus the blood level can be maintained satisfactorily by injections of this extract.

FERGUSON, Niagara Falls, N. Y.

THE CONTACT CHEMORECEPTORS OF THE HONEY BEE, APIS MELLIFERA LINN. DWIGHT ELMER MINNICH, J. Exper. Zool. **61**:375 (April 5) 1932.

The first leg and the antennae of the honey bee clearly distinguish a $^{64}/_{100}$ molecular saccharose solution from an equimolecular solution of lactose, and from water, and hence must possess contact chemoreceptors. The extent to which the third leg is sensitive to chemical stimulation is not certain. The evidence suggests that in some cases bees are able to distinguish saccharose and lactose solutions through their antennae without actual contact. The state of nutrition profoundly affects the responsiveness to antennal stimulation by saccharose solution. When

one considers bees, butterflies and flies collectively, instances of contact chemoreceptors can be found in all or practically all of the head and thoracic appendages. It is suggested, therefore, that the ancestral insect may have possessed such receptors in each of its appendages.

WYMAN, Boston.

NEW METHOD OF COMBATING PROLONGED PAIN. GEORG ZACHARIAE, Fortschr. d. Med. **50**:640 (July 22) 1932.

The author discusses the two components of pain, the physiopathologic and the psychic. The first is usually dependent on inflammatory or other pathologic changes in the region of the sensory nerves. The psychic constitution may dispose toward an expansion of the pain and infrequently to an actual unbelievable capacity to bear it. In the Frederick Müller Clinic in Munich, a drug has been used, a preparation of aconite, and the author cites cases in which the administration of from 4 to 16 drops, three times a day, gave relief from various pains which were not assuaged by salicylates, cinchophen or the coal tar derivatives. He concludes that aconite might act on the pain centers and infers that they exert an effect on the vegetative nervous system in view of the tachycardia and general anesthesia produced by aconite poisoning. He has found the drug of considerable use in migraine.

HART, Greenwich, Conn.

RESEARCH INVITES THE PSYCHIATRIC SOCIAL WORKER. INA L. MORGAN, Ment. Hyg. **16**:458 (July) 1932.

Psychiatric social work is presented by Morgan as "one of the most interesting, exacting, and fruitful fields of research, dealing with life in the living, personality in its development, and adjustment in the very process of adjusting." This research, however, requires long and patient toil, constant alertness, keen observation, accurate recording, well balanced judgment and demonstrable conclusions. The worker must have a wide horizon of thought, patience, thoroughness and inquisitiveness. She must be open-minded, tolerant and generous. Morgan suggests the three P's of research: perseverance, persistence and precision, with the slogan: "Never be content with the obvious." The goal of successfully applied psychiatric social research will be triumphant, happy living for the multitude who would otherwise sink into the mire of despair and desolation.

DAVIDSON, Newark, N. J.

THE VARIATION OF THE ANGLE OF CONVERGENCE AT A CERTAIN DISTANCE IN OBLIQUE VISION. DUPUY-DUTEMPS, Ann. d'ocul. **169**:147 (Feb.) 1932.

Dupuy-Dutemps states that the angle of convergence is studied in classic treatises only for fixation in the median plane. It varies according to the distance, increasing when the distance is decreased. In the lateral positions the angle also varies in the function of obliquity of vision. For the same distance from the point of fixation the angle of convergence decreases as the angle of deviation increases. This relation is given in the following formula:

$$\text{Tgte } G = \cos w \frac{B}{1 - \frac{B^2}{4}}$$

C represents the angle of convergence and *B*, the base line.

BERENS, New York.

PERMEABILITY OF THE MENINGES AND ABSORPTION. RISER and PLANQUES, Ann. de méd. **31**:115, 1932.

Different dyes, acetylcholine and insulin if injected into the subarachnoid space are gradually absorbed into the general circulation, although at a much slower rate than following intramuscular injections. Epinephrine is eliminated

more rapidly from the cerebrospinal fluid than following its injection into the muscles. None of the three substances, epinephrine, acetylcholine or insulin, when injected into the subarachnoid space produced any direct effect on the central nervous system or on the blood vessels—an observation that supports the theory that their point of attack is in the periphery and not in the central nervous system. It seems that these substances are absorbed via the venous system, if conclusions are allowed from observations on the absorption of dyes injected into laboratory animals.

WEIL, Chicago.

JUVENILE CRIME. ALBERT BECKHAM, J. Juvenile Research **16**:66 (Jan.) 1932.

The causes of crime among children are few but complex. The first is the plasticity of the growing organism, rendering the child unduly susceptible to influence, whether good or bad; the second is social pressure which in congested districts is often responsible for the formation of gangs; other factors are defective domestic discipline with the resulting failure of "psychologic weaning," misdirected efforts at self-support (responsible for many cases of begging and stealing), chaotic efforts at mating, poverty and in some cases feeblemindedness or psychopathic personality. The latter defects, although not the principal causes of delinquency, are important because of the relative incorrigibility of the offender of this type. The solution to the problem is the deep, intelligent understanding of the child's personality development as well as of his behavior in regard to group relationships.

DAVIDSON, Newark, N. J.

MECHANICAL COMPRESSION OF THE SPINAL CORD BY TUMOROUS LEUKEMIC INFILTRATION. HANS H. REESE and WILLIAM S. MIDDLETON, J. A. M. A. **98**:212 (Jan. 16) 1932.

The authors report two cases of infiltration of the spinal meninges with leukocytic masses and one case of multiple leukemic nodules with invasion of peripheral nerves. The first case, in which neurologic symptoms indicated a level lesion, showed at necropsy a peridural tumor which did not infiltrate the cord. There were chromatolysis of anterior horn cells, Nonne's fenestration in the right lateral and posterior tracts and other changes in the cord attributed to edema from compression. The second case is of interest from the clinical point of view because of the variability of the neurologic picture. The patient had attacks of tetraplegia with remissions. The tumor removed at operation was reported as a lymphosarcoma.

JENKINS, Indianapolis.

LESIONS OF THE MUSCLE FIBERS IN EXPERIMENTAL INTOXICATION WITH LEAD. J. M. DE VILLAVERDE, Trav. du lab. d. recherches biol. de l'Univ. de Madrid **27**:226, 1931-1932.

This paper closes a long series of publications concerning the degenerations of peripheral nerves and the central nervous system of the rabbit in experimental intoxication with lead. Saturnine degeneration of the muscle fibers cannot be compared exactly with any of the types described by M. B. Schmidt in Aschoff's "Pathologische Anatomie." In the final status, the degeneration must be called necrosis, i. e., degeneration without defensive reaction. The muscle fiber loses first the cross-striation, while the longitudinal striation becomes more apparent; later, even the latter disappears, the amount of protoplasm diminishes, and, not infrequently, vacuolation takes place.

LORENTE DE NÓ, St. Louis.

DERMATITIS FOLLOWING NERVE INJURY. RUTH HERRICK, Arch. Dermat. & Syph. **26**:879 (Nov.) 1932.

Because of the infrequency with which dermatoses follow injury of a nerve, Herrick reports such a case. Her patient, a woman, aged 27, suffered lacerations

over the left eyebrow, below the chin and at the angle of the mouth, in an automobile accident. The wound over the eyebrow bled, requiring hemostasis and apposition of the skin with clips. Although the laceration healed promptly, the patient noticed within six weeks the appearance of a vesicular rash, resembling eczema rather than herpes, over the left eye. Neither of the other two lacerations was followed by an eruption. The area of the dermatosis corresponded to that of the distribution of the supra-orbital branch of the fifth nerve and was presumably of neural origin. Treatment had no effect.

DAVIDSON, Newark, N. J.

THE SIGNIFICANCE OF URINARY "PROTEOSE" IN IDIOPATHIC EPILEPSY. R. L. H. MINCHIN, Brit. M. J. **2**:97 (July 16) 1932.

Sixty-eight unselected cases of idiopathic epilepsy were used for this study. All treatment was temporarily stopped. In 71 per cent of the cases, proteose was found in the urine. The proteose was extracted and injected in dilution into an arm in ten cases. A similarly diluted volume of sodium hydroxide was injected into the other arm. In no case was erythema more intense in one arm than in the other. Subcutaneous injections were made at weekly intervals. The results were either nil or questionable. The author remarks that no definite conclusion can be drawn. When an epileptic patient has a bout of fits, the urine is at first loaded with proteose, which disappears with the seizures. This suggests that the fits "discharge" the subject by causing the body to destroy the circulating convulsant toxin.

FERGUSON, Niagara Falls, N. Y.

SKULL AND BRAIN TRAUMAS: THEIR SEQUELAE. A CLINICAL REVIEW OF TWO HUNDRED AND FIFTY-FIVE CASES. MARK ALBERT GLASER and FREDERICK P. SHAFER, J. A. M. A. **98**:271 (Jan. 23) 1932.

Subjective complaints follow 80 per cent of injuries to the brain and are more frequent in older patients. Headache and dizziness are the commonest of these sequelae. The latter symptom is classified as true or rotary vertigo, postural dizziness and general dizziness. Vestibular tests invariably demonstrate pathologic changes in the first two, but less frequently in the last named type. Neurologic signs occur in 32.5 per cent of cases, diminished hearing being the most common sign. Recovery from traumas of the first, second and eighth nerves is less common than recovery from other cranial nerve injuries. Convulsive states occurring from one to two months after an injury are apt to be functional, whereas those appearing from eight months to five years later are of organic origin.

JENKINS, Indianapolis.

THE TREATMENT OF MENTAL DISORDERS BY PYREXIA PRODUCED BY DIATHERMY. C. B. BOMFORD, Lancet **2**:337 (Aug. 13) 1932.

Hyperpyrexia was induced in twenty-one psychotic patients by high frequency currents passed through the body. Usually, twelve biweekly treatments were given. There is no evidence that pyrexia produced in this way is more effective in causing a clinical remission than malaria. There are, however, several apparent advantages. The patient is under complete control throughout the treatment. Prolonged treatment does not produce physical prostration or weakness. Furthermore, it is possible to give this mode of treatment to aged or to debilitated patients. On the other hand, there is great danger of burning patients who are either restless or uncooperative.

BECK, Buffalo.

POST-VACCINAL ENCEPHALITIS. A. H. GORDON and LAWRENCE J. RHEA, Am. J. M. Sc. **184**:104 (July) 1932.

With a clinical and pathologic report of a case of postvaccinal encephalitis, the authors discuss the differentiation between this disease and poliomyelitis and

epidemic encephalitis. The specific, characteristic lesions of postvaccinal encephalitis are the areas of demyelinization in the spinal cord and, microscopically, a meningo-encephalitis. The demyelinization seems to be the primary lesion, and cellular infiltration is secondary. The incubation period between vaccination and the development of symptoms is most often from ten to fourteen days. In severe types of vaccinia, and especially in those complicated with nervous disturbances, the serum of recently vaccinated persons should be administered.

MICHAELS, Boston.

PERSISTENT EXOPHORIA AFTER CRANIAL CONCUSSION. JEAN SÉDAN, Rev. d'oto-neuro-opht. **10**:679 (Nov.) 1932.

About two weeks after a blow on the head which rendered him unconscious, a man, aged 24, began to have difficulty in reading. Examination revealed normal vision and a normal visual apparatus. After reading for five minutes, divergence of the globes began, and convergence was impossible. Rest of the eyes for fifteen minutes put all in order again. No evidence was found, even with the use of atropine, of hypermetropia. Undoubtedly, the trauma produced some disturbance of the coordinating center for convergence. Morax classified heterophoria among the manifestations of ocular neurasthenia and thought that ocular or general traumatism is not rarely the provocative cause of an attack of ocular neurasthenia.

DENNIS, Colorado Springs, Colo.

THE EVOLUTION OF EDEMA IN CHOKED DISK. E. DUHAMEL, Ann. d'ocul. **169**: 656 (Aug.) 1932.

Duhamel studied the localization of edema in three recent cases of choked disk. In one case stasis occurred seven days before autopsy, and in another case fifteen days before autopsy. In the third case the time could not be determined, but vision in the eye with papilledema was still normal four days before death. The author concludes from the pathologic examination of the optic nerves that edema begins in the papilla; that it tends to ascend toward the brain; that its progress is arrested for a certain time by the lamina cribrosa, and that it then diffuses the length of the perineurium and the central vessels, but that edema in this location occurs relatively late in the evolution of choked disk.

BERENS, New York.

AN ANALYTICAL STUDY OF VARIOUS FACTORS RELATING TO JUVENILE CRIME. EDWARD RUGGLES, J. Juvenile Research **16**:125 (April) 1932.

In order to determine the factors relating to juvenile crime, Ruggles has studied the records of 103 inmates of a North Carolina juvenile prison farm. He finds that, age for age, they are below average both in abstract intelligence and in mechanical aptitude. The boys who did achieve high scores in the latter were the boys who committed crimes (such as stealing or tampering with an automobile) which required a mechanical intelligence. Boys guilty of sodomy, rape and seduction generally had inferior intelligence even for the boys on the farm, while those arrested for bigamy tended to have higher scores. In almost every case a broken or unhappy home was found.

DAVIDSON, Newark, N. J.

LATERAL SYNDROME OF THE MEDULLA (OCCLUSION OF THE POSTERIOR CEREBELLAR ARTERY: VASCULAR LESIONS OF THE HIND BRAIN). A. CREIG ANDERSON, R. D. LOCKHART and W. CLARK SOUTER, Brain **54**:460 (Dec.) 1931.

The patient, a man, aged 62, exhibited complete inability to swallow solids or fluids, Horner's syndrome on the right side, paralysis of the right side of the palate, defective sensation of taste on the right side of the tongue, abolition of the nausea reflex and defective sensibility to pain and temperature. The various clinical features are reviewed critically in relation to previous studies of the

swallowing reflexes and the nervous supply to the esophagus. The authors suggest: (1) a lesion which was just sufficient to cause irritation of the dorsal vagus nucleus, with resulting spasm of the esophageal entrance, and (2) interruption of the sensory motor reflex (in the region of the cricoid cartilage), so that no inhibition was placed on the dorsal nucleus to cause its relaxation in this area.

MICHAELS, Boston.

THE RUDIMENTARY PARIETAL ORGAN (CORPUSCULUM PARIETALE). ALFRED ALEXANDER, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **34**:252, 1932.

In 25 per cent of the human embryos examined by Alexander a small nodular formation was found approximately in the midline of the commissura habenularum, the structure of which corresponds to that described by Krabbe as the corpusculum parietale in mammals. In man the anlage for this structure makes its appearance during the second half of intra-uterine development. In all probability the nodule exists for only a short period, after which it begins to regress. It would seem that in some cases the anlage persists and, owing to its immaturity, goes on to neoplastic formation. This, according to Alexander, may explain the origin of some tumors in the region of the pineal gland.

KESCHNER, New York.

ACTIVE EXTERNAL HYDROCEPHALUS. W. J. GARDNER, J. Nerv. & Ment. Dis. **75**:601 (June) 1932.

Three cases in which the diagnosis was active external hydrocephalus are described. This diagnosis was made on the basis of the encephalographic finding of marked dilatation of the subarachnoid space over the cerebral hemisphere. Symptoms of headache, vomiting and failing vision led to the preoperative diagnosis of tumor in two of the cases. The activity of the process was indicated by the symptoms of increased intracranial pressure and choking of the optic disks in each case. The total volume of cerebrospinal fluid was found to be markedly increased, but the cause of this increase was not determined. In each case simple subtemporal decompression was followed by complete recovery.

HART, Greenwich, Conn.

SPINAL ANESTHESIA IN VASOSPASTIC DISEASES OF THE LOWER LIMBS. E. D. TELFORD and J. S. B. STOPFORD, Brit. M. J. **1**:1116 (June 18) 1932.

In circulatory disturbances of the limbs it is necessary to determine the degree of vascular disease and also the extent of any vasospasm which is superimposed on the completely or partially occluded vessels. By means of a spinal anesthetic, which will take effect as high as the sixth dorsal segment, the whole of the sympathetic supply to the lower limbs can be temporarily cut off. This will do for an hour exactly what a lumbar sympathectomy will do permanently. The test is of vital importance in any case of thrombo-angiitis obliterans in which sympathectomy is being considered, since this operation can only relieve vasospasms and has no effect on any element of thrombosis present.

FERGUSON, Niagara Falls, N. Y.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

TRACY J. PUTNAM, M.D., *Secretary*

Regular Meeting, Oct. 19, 1933

E. S. ABBOT, M.D., *Presiding*

PATHOLOGIC FINDINGS IN THE HYPOTHALAMUS IN THE PSYCHOSES. DR. NAOMI RASKIN.

From a study of the hypothalamic region in cases of different psychoses, I conclude that in none of the described psychic entities are there lesions in the hypothalamus which are specific, comparable for example to those in Wilson's lenticular degeneration.

DISCUSSION

DR. A. MYERSON: Dr. Raskin made sections of the hypothalamus from one end to the other. An important fact is that symptoms were not many in comparison with the lesions. One would expect much more disturbance, although vegetative symptoms are not looked for with any degree of zeal in state or other hospitals. It is the duty of clinicians studying dementia paralytica, for example, to investigate these aspects more thoroughly. Anatomy and physiology should be more closely linked to the clinical aspects of the hypothalamic functions. It is noteworthy that the supra-optic nuclei have the richest vascularity of any part of the nervous system.

DR. T. J. PUTNAM: Did your observations bear out the conclusions of Popa and Fielding? There is doubt as to the finality of their observations in view of the general scheme of the cerebral circulation demonstrated by Pfeifer.

DR. N. RASKIN: The venous supply of the supra-optic nuclei is exceedingly rich. My observations do seem to accord with the findings of Popa and Fielding. My pathologic material was selected and I did not find such striking clinical differences. In dementia paralytica, both the supra-optic and the ventricular nuclei are affected. As for the venous supply as I saw it, I am ready to admit Popa and Fielding's findings. Perhaps the vascularity of these two nuclei is responsible for their being so susceptible to disease. The cortical control is in some way interrupted. It seems possible that serial section by Weigert and Bielschowsky stains, which have just been started, will tell more.

COMPONENTS OF CEREBROSPINAL FLUID PRESSURE AS AFFECTED BY CHANGES IN POSTURE. DR. JULIUS LOMAN.

Many physical phenomena of the craniovertebral cavity may be understood by the pressure reactions of the cerebrospinal fluid to postural alterations. In the present study my associates and I were concerned with: (1) observations of the relationship of the cisternal and lumbar pressures in certain postures, and (2) an evaluation through these observations of the components of the pressure of the cerebrospinal fluid. Light was thrown particularly on the importance of the effect of gravity in its contribution to the pressure of this fluid.

When the pressure of the cerebrospinal fluid was expected to be positive, the ordinary Ayer or Fremont-Smith manometer was utilized. For the measurement of negative pressures, an original manometric system was used. This consists

of an air pressure control chamber and a U-shaped water manometer, which is connected by means of rigid rubber tubing to a pipe-stem manometer, stopcock and needle. In order to cause the fluid to rise in the pipe-stem manometer (when the subarachnoid pressure is negative), the pressure of the air within the system is lowered beforehand by means of a syringe connected with the air chamber. The pressure of the cerebrospinal fluid is calculated by subtracting the reduction in air pressure from the reading in the straight manometer.

Combined lumbar and cisternal punctures with the subject in the sitting position were first performed in a series of fourteen cases of various types of mental disease. The following observations were made: 1. The lumbar pressures ranged from 375 to 565 mm. of water. 2. The cisternal pressures ranged from a positive one of 40 mm. to a negative one of 85 mm. of water. 3. There was a close relationship between the lumbar pressure and the vertical lumbar-cisternal distance. 4. The difference between the lumbar and cisternal pressures (L — C) was equal or practically equal to the vertical lumbar-cisternal distance. 5. From the knowledge of the vertical distance and one of the two pressures the other pressure is easily determined by the simple formula: $CP = LP - D$ or $LP = D + CP$ (when CP equals the cisternal pressure, LP equals the lumbar pressure, and D, the vertical distance).

In the second series of observations (fifteen cases) the lumbar pressures in the lateral recumbent and sitting positions were compared with the lumbar-cisternal distances. From these observations it was noted that: 1. The sum of the pressure in the lateral recumbent position and the vertical lumbar-cisternal distance is much greater than the corresponding figure for the lumbar pressure in the sitting position. 2. There is no regular correlation between the two pressures, for in some cases a low pressure in the lateral recumbent position is coupled with a high pressure in the sitting position and *vice versa*. 3. These observations indicate that these two pressures are to a large extent independent of each other and that they are respectively composed of different components. 4. The fact that the pressure at the lumbar subarachnoid space in the sitting position approximates the vertical lumbar-cisternal distance further indicates that this pressure is dependent mainly on the height of the spinal fluid above the site of the puncture.

In the third series of observations reading of the cisternal and lumbar pressures in the sitting position following successive extractions of 10 cc. of spinal fluid were compared with the lumbar-cisternal distance. The observations follow: 1. With each extraction of fluid, both pressures diminished so that the figure for L — C noted in the first series of experiments equalled or practically equalled the lumbar-cisternal distance. 2. Although the fluid was removed from the lumbar subarachnoid space quite rapidly and so that the cisternal pressure reached a very low figure, the subjects complained of no disagreeable symptoms, such as headache, dizziness or weakness.

In the next series of observations the subjects were placed on their hands and knees so that the occiput and spine were in horizontal alinement. This position was chosen to eliminate all gravitational effects on the cerebrospinal fluid and the blood. In a study of fifteen subjects it was found that: 1. In the hands-and-knees position the pressure was considerably lower than the corresponding pressure in the lateral recumbent position, whether the pressures were measured at the lumbar or at the cisternal regions. 2. The average pressure in the hands-and-knees position was 40 mm. as compared with 122 mm. of water for the lateral recumbent position.

The observations cited indicate that: 1. The difference in pressure in the two positions mentioned is due to differences in hydrostatic and elastic responses of the venous column of blood in relationship to the vertebral canal. 2. In the sitting position the pressure of the cerebrospinal fluid is mainly due to the height of the column of spinal fluid above the site of puncture. Apparently, all other forces compensate each other. 3. Because of the marked difference in pressure of the cerebrospinal fluid occurring from positional alteration the craniovertebral system

can no longer be regarded as a completely closed box. To consider it so is to hold a point of view altogether too simple when applied to the physical make-up of the human craniospinal cavity.

DISCUSSION

DR. D. GREGG: Were the results recorded obtained from punctures made simultaneously in the lumbar and cisternal regions? Second, if flexible tubing is used is there not an absolute loss of pressure, although this loss may be a constant factor and may not confuse the results? Third, when a patient is lying on the side, is not the increased positive pressure from vessels above the midline more or less balanced by the negative pressure from vessels lying below the midline?

DR. J. LOMAN: The determinations of pressure in the various positions were done successively on each patient. The apparatus for recording negative pressure was checked for its accuracy as follows: If the pressure of the cerebrospinal fluid in the lateral position was found to be 50 mm. of water, by reducing the atmospheric pressure within the air chamber so that the cerebrospinal fluid rose to 250 mm., for example, the actual pressure by calculation was still seen to be 50 mm. The tubing used in the apparatus is practically rigid, so that no error due to elasticity is introduced into the determination of the pressure. From a purely hydrostatic point of view, we do not believe that in considering the factors determining the pressure in the lateral recumbent position the veins below the level of the spinal canal have any effect due to suction or that their pressure counteracts the hydrostatic effects of the veins acting downward on the spinal canal. Another factor must, however, be considered; that is, the hemodynamic effect or the effect of the flow of blood on the pure hydrostatic venous component. It may be that this hemodynamic effect equalizes the hydrostatic effect of the venous blood acting downward on the spinal canal.

In the hands-and-knees position all the venous forces are acting downward toward the abdomen, hence the low pressure of the cerebrospinal fluid.

DR. FRANK FREMONT-SMITH: These observations form the first adequate series of data on the pressure of the cerebrospinal fluid in the horizontal and upright positions. Dr. Loman's observations concerning the relationship of lumbar and cisternal pressure in the upright position to the height of the column of fluid between these points is a confirmation from a slightly different point of view of the observations made some years ago by Dr. Solomon and Dr. Ayer, demonstrating that in any position the level of the fluid in manometers in lumbar, cisternal and ventricular needles is the same. As regards the influence of the columns of venous blood above and below the spine in the lateral recumbent position, I think that these two columns tend to counterbalance each other as Dr. Gregg has suggested. I find it difficult to accept the pressure of the cerebrospinal fluid in the hands-and-knees position as being more basal than that in the lateral recumbent position. The hands-and-knees position adds many complicating factors which are difficult to evaluate. First, there is the drainage of venous blood into the pendant arms and legs, and perhaps also into the abdomen. This tends to lower the venous pressure and therefore also the pressure of the cerebrospinal fluid, but a lower pressure is not necessarily more basal. Furthermore, the hands-and-knees position undoubtedly influences respiration, a factor which will have to be evaluated. I think that one should pay more attention to a standard pressure, i. e., a pressure measured under well defined and easily duplicated conditions, than to a so-called basal pressure which will depend to a considerable extent on the definition of "basal." I wish to ask how, in determining the pressure in the hands-and-knees position, the zero point is reached?

DR. J. LOMAN: In the hands-and-knees position, the needle being perpendicular to the plane of the back becomes part of the manometric system, and its length must be considered in the calculation of the pressure. Since the fluid level in all cases was down in the needle, it was necessary to use the attachment for negative pressure to obtain the zero point. The final pressure was determined as already described in the body of the paper.

EFFECTS OF INSULIN AND AMYTAL ON INTRACRANIAL CONDITIONS AND METABOLISM. DR. WILLIAM DAMESHEK.

An attempt was made to study the mechanism of the neurologic symptoms of insulin hypoglycemia in man, chiefly by comparing the contents of dextrose and oxygen in the vessels supplying the brain and the arm before and after the intravenous administration of insulin. Samples of blood were obtained as nearly simultaneously as possible from the brachial artery, internal jugular vein and (usually) from a basilic vein; they were analyzed for content of dextrose, oxygen, carbon dioxide and (frequently) lactic acid. Usually the pressure of the arterial blood, the pressure and dextrose content of the spinal fluid, the pulse rate and the associated symptoms of the hypoglycemic reaction were studied.

The following results were obtained: 1. The chemical changes in the blood usually varied directly with the severity of the reaction. 2. The uptake of dextrose by the brain (as measured by the difference in the dextrose content of an artery and that of the internal jugular vein) became materially reduced during the severe hypoglycemic reaction, although that of the arm usually became increased. 3. The uptake of oxygen by the brain (as determined by arteriovenous differences in oxygen content) varied directly with the severity of the insulin reaction, becoming markedly reduced during the most severe reactions. 4. The lactic acid of the blood became increased during the reaction, no differences between vessels being noted. 5. The pressure of the spinal fluid regularly became increased before the objective phenomena of the hypoglycemic reaction could be seen; there was no essential change in the dextrose content of the spinal fluid during the period of observation (from forty-five to ninety minutes). 6. The pressure of the pulse usually became increased, owing to a slight rise in systolic pressure and to a more marked fall in diastolic pressure.

When the effect of an injection of epinephrine was superimposed on the insulin reaction the symptoms of the insulin reaction were regularly diminished.

Various theories explaining the neurologic symptoms of the hypoglycemic reaction are discussed, and the epinephrine theory is critically analyzed.

The marked diminution in the arteriovenous difference in content of oxygen during the severe insulin reaction may signify an actual diminution in oxygen uptake by the brain and arm. If this is true, the neurologic symptoms of the insulin reaction may be due to the effects of lack of oxygen on the tissues of the brain.

DISCUSSION

DR. WILLIAM LENNOX: The use of the expression "uptake of oxygen by the brain" may be misleading. Venous blood which becomes more like arterial blood (as happened with the blood of the internal jugular vein during hypoglycemic reaction) may be due to an increased flow of blood through the brain and not to an altered metabolism of the brain. The increase in the pressure of the blood and spinal fluid that was observed would indicate a dilatation of cerebral blood vessels which would cause an increased flow of cerebral blood. Mrs. Gibbs and I obtained somewhat similar changes in blood gases when we had patients breathe air containing 10 per cent of carbon dioxide. It seems perilous to make suggestions concerning the rate of consumption of oxygen or sugar by the brain without coincident observations of the blood flow.

DR. ABRAHAM RUDY: In the absence of other symptoms loss of memory has been observed in cases of hypoglycemia. I believe that a number of the symptoms of the insulin reaction are caused by the hypersecretion of epinephrine. Through the increase of the dextrose in the blood, epinephrine helps to abolish these and other symptoms of the insulin reaction. There are two stages in the insulin reaction.

The first stage is brought about by the hypersecretion of epinephrine and the second stage is the result of the effect of the low blood sugar on the central nervous system. The increase in the consumption of oxygen in the brachial artery may be due to the muscular twitchings.

DR. WILLIAM DAMESHEK: Dr. Lennox' and Dr. Rudy's points are well taken. However, our experiments show that the neurologic symptoms are due to a lack of oxygen rather than to an increase in circulating epinephrine or to a diminution in dextrose alone.

A REVIEW OF THE RESEARCHES CONDUCTED BY THE INTERNAL JUGULAR PUNCTURE METHOD.

Puncture of the internal jugular vein was introduced in 1927 for the purpose of making possible a direct study of the metabolism of the brain. The working hypothesis underlying its introduction was that examinations of spinal fluid, invaluable as they are for the understanding of certain pathologic conditions, are incapable of bringing a direct understanding of the physiology of the brain, since the spinal fluid is only a passive participant in the activity of the brain.

Gaseous Interchange in the Brain: Through the work of Lennox and his colleagues, as well as that of the group of the Boston State Hospital, it has been shown that the respiratory quotient of the brain is somewhat higher than that of the arm or leg, that more oxygen disappears in the circuit from artery to vein through the brain than in a similar circuit through the leg and arm.

Use of Sugar: Similarly, more sugar disappears in the transit from artery to vein through the brain than in that through the leg or arm. Less sugar disappears under ether anesthesia than under ordinary conditions, although the significance of this is not known.

Intracranial Pressures: By combined study of the pressures of the artery, the jugular vein and the spinal fluid spaces and by the use of experimental postural conditions and drugs it has been possible to reach certain conclusions about the interrelationships of these three components of intracranial dynamics. Posture exercises a direct and immediate effect on all the pressures within the cranial cavity. The hydrostatic conditions are those of a tube containing fluid. Changes of respiration, effort, straining as at stool, etc. cause marked changes in cerebral, arterial, venous and spinal fluid pressures. There is no direct relation between the jugular venous pressure and the pressure of the spinal fluid, although under ordinary conditions they undergo similar fluctuations. However, the pressure of the spinal fluid may rise sharply or fall without there being a similar rise or fall in the venous pressure. Thus, with administration of histamine, the pressure of the spinal fluid rises sharply, whereas the jugular venous pressure remains unaltered. Caffeine operates to lower the pressure of the cerebrospinal fluid, the arterial and venous pressure remaining fundamentally unaltered.

It is probable that vasodilatation and vasoconstriction are the chief factors which, in the case of the drugs used, create changes in the pressure of the spinal fluid, vasodilatation creating an increase of pressure and vasoconstriction a decrease of pressure. The arterial pressure has no direct relation to the pressure of the cerebrospinal fluid or, in some instances, to the venous pressure. My associates and I have recorded cases in which arterial pressure has risen and fallen without any change in the pressure of the spinal fluid or that of the venous blood.

While the osmotic tension is undoubtedly a factor in the intracranial dynamics and pressures, it changes too slowly to operate in our experiments, although the work done with hypotonic solutions shows that its rôle can be made experimentally significant.

Blood Flow: With the collaboration of F. A. Gibbs and the use of his ingenious electrothermic device we have been enabled to measure the flow of blood through the brain in most cases by inserting the electrothermic needle through the jugular vein, and in fewer cases by inserting it into the internal carotid artery high up in the neck. Incidentally, we have found that the internal carotid artery can be punctured without any injury whatever and gives results of importance in understanding intracranial conditions.

With the patient passive and moved into various planes by means of a table, the flow of blood definitely changes in speed, although we are not as yet prepared to say that the change is regular and invariable. It is certain, however, that posture is of direct and immediate importance, and our experiments show that the speed is exquisitely responsive to all manner of changes.

We have just commenced to make a study of the effects of drugs. It is noteworthy that amytal produces no change of any importance in the rate of the flow of blood, while ether exercises an influence in this direction. As an example, in the results which have been obtained we may contrast ether and amytal in their effect on intracranial conditions. Ether increases the pressure of the cerebrospinal fluid and increases the venous pressure; it decreases the amount of oxygen consumed by volume and similarly changes the metabolism of the skull; it alters the rate of the flow of blood to the brain profoundly. On the other hand, amytal exercises no important influence on the pressure of any of the intracranial components; it does not affect the chemical interchange and does not alter the flow of blood. In anesthetic doses, however, it lowers metabolism profoundly and probably exercises a direct localized neuronic effect. With our present technic it is possible to measure the interchange of gases and sugar which takes place with any drug and its simultaneous effect on the venous, arterial and spinal fluid pressure and on the flow of blood through the brain.

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